evaporation and the residue dissolved in a small amount of EtOH. To the solution was added Et_2O and the product was collected by filtration and recrystallized from EtOH to give 86 mg of **9e** (see Table III).

5-Iodo-2′-deoxycytidine (IdC) and 5-iodo-2′-deoxyuridine (IdU) were commercial samples obtained from Sigma Chemical Co., St. Louis, Mo. *ara*-IC was synthesized according to Honjo et al.[15] *ara*-IU (**4e**) was prepared according to Hunter.[16]

Antiviral Assay. Vero cell monolayers were infected with approximately 1 plaque-forming unit (PFU) per cell of herpes simplex virus type 1 (HSV-1) strain 2931 and incubated for 2 h. Maintenance media containing the various concentrations of drugs were used to overlay the monolayers. Supernatant fluids were collected 24 h later and titered on Vero cell monolayers as described previously.[17] Percent inhibition over controls was calculated.

Cell Culture Studies (by Dr. J. H. Burchenal). The technique of Fischer[18] was employed with modifications.[19] Mouse cell lines L5178Y and P815 were incubated in McCoy's medium with 15% fetal calf serum. The initial inoculum was 40 000–60 000 leukemic cells/mL. For growth inhibition studies, 0.1 mL of a 50-fold concentration of the nucleoside in question was added to 5 mL of the cell-containing media. The tubes were set up in triplicate, loosely capped, and allowed to incubate in 5% CO_2 at 37 °C for 96 h. Growth to $\sim 10^6$ cells/mL occurred in the control tubes. The contents of each tube was counted on a Coulter counter and the percentage of inhibition of growth was calculated.

Acknowledgment. The authors are indebted to Dr. J. H. Burchenal and Kathy Kalaher for the cytotoxicity data on L5178Y and P815 cells in culture and to Tom Livelli for expert technical assistance with the herpes virus assays.

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Preparation of the Enantiomeric Forms of 9-(5-Deoxy-α-*threo*-pent-4-enofuranosyl)adenine and 9-(3,5-Dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine and in Vitro Antileukemic Screening

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The preparation and use of 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose and 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-arabinofuranose in the synthesis of the L and D forms of 9-(5-deoxy-α-*threo*-pent-4-enofuranosyl)adenine, respectively, are described. The preparation of 9-(3,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine (**19**) was accomplished from either 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose or 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose. In each case, acetolysis was performed to obtain the acetates which were condensed with 6-(benzamidochloromercuri)purine by the titanium tetrachloride method. Treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene and removal of the blocking groups produced the desired nucleosides. Only **19** showed inhibitory activity toward leukemia L1210 in vitro.

The nucleoside antibiotic decoyinine (angustmycin A) was reported to have antibacterial and antitumor activity.[1] The structure of decoyinine was shown to be 9-(6-deoxy-β-D-*erythro*-hex-5-enulofuranosyl)adenine.[2] The closely related compound which lacked the anomeric hydroxymethyl group, 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine, was shown to inhibit *Streptococcus faecalis* with the same potency as decoyinine.[3] In order to further explore the biological effects of 4′,5′ unsaturation in nucleosides and to possibly improve upon the range and extent of biological activity, this laboratory set out to prepare a number of compounds in this series.

Previous reports from this laboratory have described the synthesis of several 4′,5′-unsaturated nucleosides.[4,5] Originally the synthesis of such unsaturated nucleosides was undertaken starting from a preformed nucleoside.[4,6] It became evident in time that synthesis by this route created a number of problems, among which were cyclonucleoside

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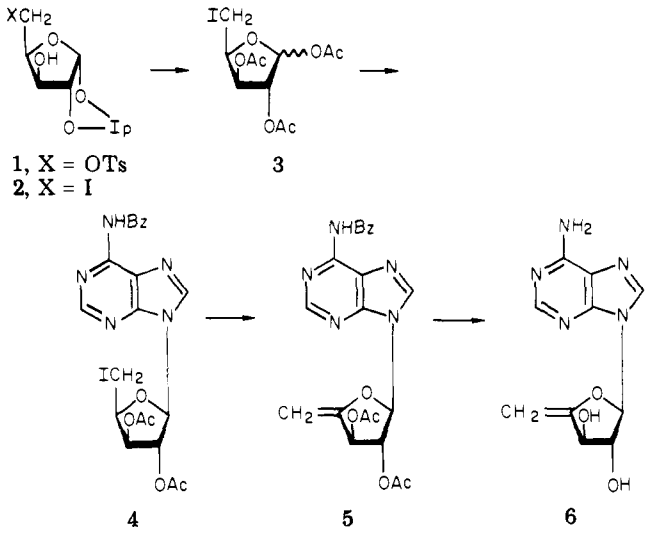
Scheme I



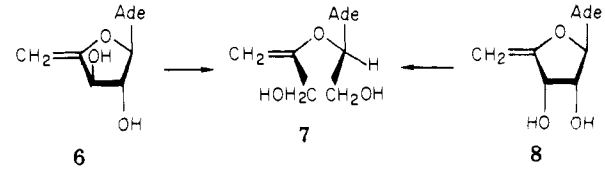
Ip = $C(CH_3)_2$; Ac = acetyl

formation during substitution or elimination reactions or difficulties in the selective removal of acid labile blocking groups without corresponding hydrolysis of the nucleoside C–N bond.[5] Since many of the analogues required synthesis of the corresponding nucleosides from the appropriate sugars and bases, the idea was conceived to utilize sugar derivatives of a type that could be used later to prepare the 4′,5′-unsaturated nucleosides.[5] The use of ester blocking groups facilitated their removal under mild alkaline conditions, and the purine was in a form that discouraged cyclonucleoside formation. A similar idea was conceived by Prisbe et al.[7] who succeeded in the synthesis of several nucleosides by this pathway. Previously, the synthesis of the enantiomeric forms of 9-(5-deoxy-β-*erythro*-pent-4-enofuranosyl)adenine was reported.[5]

The preparation of 9-(5-deoxy-α-L-*threo*-pent-4-enofuranosyl)adenine (**6**) began from 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-xylofuranose[8] (**1**) which was treated with NaI in 2-butanone to give 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**) (Scheme I). Acetolysis of **2** gave an anomeric mixture of acetates **3**, which was coupled with 6-(benzamidochloromercuri)purine by the titanium tetrachloride procedure.[5,9,10] The blocked nucleoside **4** was partially purified by column chromatography and then treated with 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) in DMF. The blocked unsaturated nucleoside **5** was not purified but was treated directly with NH_4OH in MeOH to remove the blocking groups. Nucleoside **6** was obtained in pure, crystalline form after chromatography on an ion-exchange column.

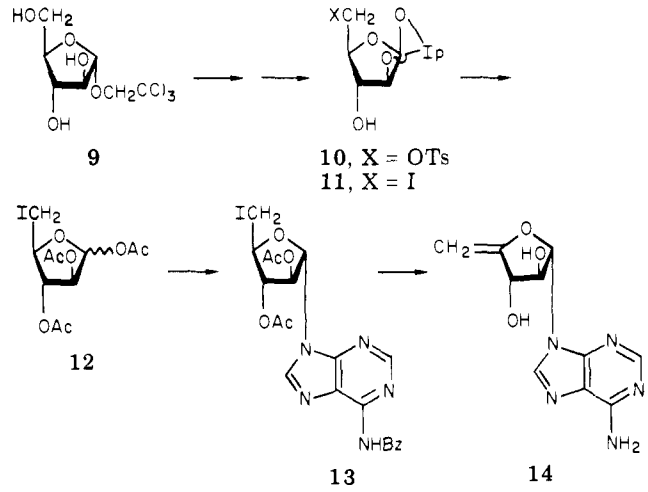
The UV spectrum confirmed that **6** was a nucleoside substituted at N-9 of adenine. The NMR spectrum supported the proposed structure, and, in particular, the 5′-CH_2 group was clearly defined. The only problem was that the NMR spectrum did not establish the configuration at the anomeric carbon atom. It is generally accepted that unequivocal determination of anomeric configuration in which H-1′ and H-2′ are oriented trans to each other requires a coupling constant less than 1 Hz;[11] the $J_{1',2'}$ for **6** was 2.8 Hz. Therefore, a polarimetric method was used to prove the anomeric configuration.[12] Nucleoside **6** was treated with $NaIO_4$ and the resulting dialdehyde was reduced with $NaBH_4$ to the dialcohol **7** (Scheme II). The specific rotation of this solution was +59°. When 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine[5] (**8**) was

Scheme II



Ade = adenyl

Scheme III



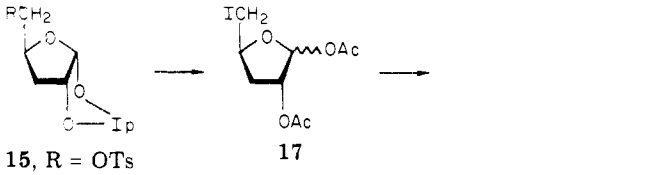
treated in a similar manner, the specific rotation was +55°. The anomeric configuration of **8** was already known since it had originally been synthesized from adenosine.[3] These results indicated that the absolute configuration at the anomeric carbon atom of **6** was the same as **8**; therefore, **6** had the α-L configuration.

The preparation of 9-(5-deoxy-α-D-*threo*-pent-4-enofuranosyl)adenine (**14**) (Scheme III) started from (2,2,2-trichloroethyl)-α-D-arabinofuranoside (**9**), prepared from D-arabinose as described by Kalvoda et al.[13] The preparation of 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-arabinofuranose[13] (**10**) from **9** was altered somewhat from the original due to difficulties encountered during the workup and purification. Treatment of **10** with NaI in 2-butanone gave 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-arabinofuranose (**11**). The preparation of **14** from **11** was carried out in an almost identical manner as the preparation of **6**, and it had identical physical properties except for the sign of the optical rotation.

The preparation of 9-(3,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine (**19**) was accomplished by two routes (Scheme IV). Route A had one early reaction that resulted in a very low yield. Route B was preferred because of higher yields of intermediates and less purification by chromatography was necessary. 3-Deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-*erythro*-pentofuranose[14] (**15**) was prepared from 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (route A). Treatment of the latter with potassium thioacetate gave 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose[11] in lower than 20% yields and required extensive chromatography for purification. The reduction of the thioacetate with Raney nickel and selective hydrolysis gave 3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose.[15] Periodate oxidation, followed by reduction of the aldehyde, afforded 3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose,[14,16] which was tosylated to give **15**.[14] Treatment of **15** with NaI in 2-butanone gave crystalline 3,5-dideoxy-5-iodo-1,2-*O*-iso-

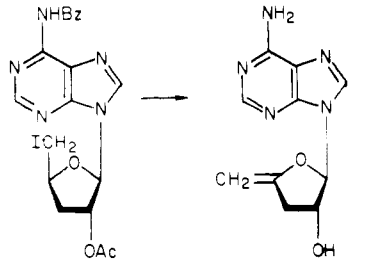
Scheme IV

route A



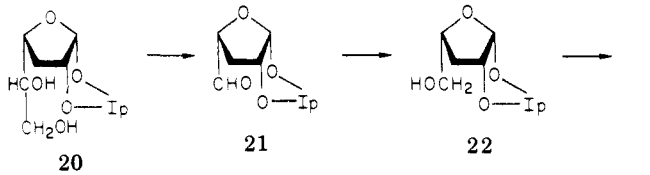
15, R = OTs
16, R = I

17

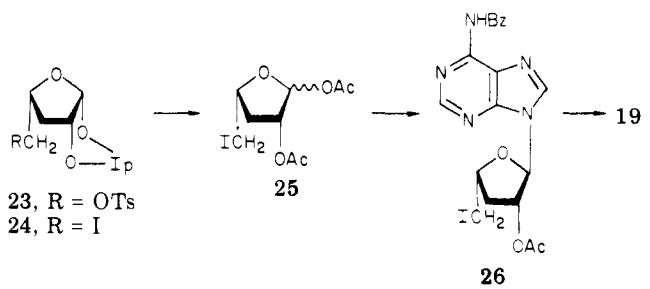


18 **19**

route B



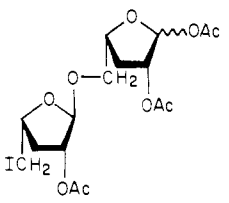
20 **21** **22**



23, R = OTs
24, R = I

25

26



27

propylidene-α-D-*erythro*-pentofuranose (**16**). Acetolysis of **16** gave the diacetate **17** which was condensed with 6-(benzamidochloromercuri)purine by the titanium tetrachloride method. The same general reactions and methods already described gave a 15% yield of nucleoside **19**.

The starting material for route B was also 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose. 3-Deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**20**) was obtained in three steps by the procedure described by Prokop and Murray.[10] Periodate oxidation[10] of **20** gave the aldehyde **21** and reduction[16] with Raney nickel in ethanol afforded 3-deoxy-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (**22**). Tosylation of **22** afforded 3-deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-L-*threo*-pentofuranose (**23**) and treatment of the latter with NaI in 2-butanone gave crystalline 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (**24**). Acetolysis of **24** gave **25** which was coupled with the base and the same reaction sequence was carried out again to give **19**. The anomeric configuration of **19** was designated as β-D based upon the coupling method used to prepare it and the low coupling constant for the anomeric proton in the NMR spectrum, which is consistent with a trans arrangement for the protons at C-1′ and C-2′.

During the chromatographic purification of blocked nucleoside **26**, a small amount of a faster moving component was isolated. The elemental analysis and NMR spectrum suggested that this was the blocked disaccharide **27**. This substance could have been formed by a standard glycoside synthesis if part of the titanium tetrachloride sugar complex had been hydrolyzed due to the presence of some moisture. It is possible that this reaction could have occurred when aqueous sodium bicarbonate solution was introduced into the reaction mixture. The bicarbonate would neutralize any acid released while the blocked sugars would have greater contact with each other in the organic phase than they would with water. We had previously noticed similar products as a result of these reactions but have never had one separate as a single component before this. Keller et al.[17] have also demonstrated that a major byproduct of nucleoside synthesis in the presence of mercury salts is a disaccharide.

The ability of the new nucleosides 6, 14, and 19 to inhibit leukemia L1210 in vitro showed that only **19** was active.[18] Growth was inhibited by 50% at a concentration of 5×10^{-5} M in this case. Two previously prepared 4′,5′-unsaturated nucleosides, 9-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine[4] and 9-(5-deoxy-β-L-*erythro*-pent-4-enofuranosyl)adenine,[5] also had no activity.

Experimental Section[19]

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose (2). A solution containing 34 g (99 mmol) of 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-xylofuranose[5] (**1**) in 250 mL of 2-butanone was treated with 25 g (170 mmol) of NaI and the mixture was heated under reflux for 24 h with stirring. Insoluble sodium *p*-toluenesulfonate was removed from the cooled mixture by filtration, and the solvent was evaporated to yield an oil. The oil was dissolved in 150 mL of chloroform and washed with 100 mL of sodium thiosulfate solution and then with H_2O (3 × 150 mL). The solution was dried ($MgSO_4$) and the $CHCl_3$ evaporated to give a syrup. Crystallization of **2** from ethyl ether *n*-hexane afforded 26.5 g (89% yield): mp 106–108 °C; $[\alpha]^{26}_D$ 39.2° (c 1, $CHCl_3$) [lit.[20] mp 108–109 °C; $[\alpha]^{22}_D$ 40.0° (c 2, $CHCl_3$)].

9-(5-Deoxy-α-L-*threo*-pent-4-enofuranosyl)adenine (6). To a mixture containing 10 g (33 mmol) of **2**, 24 mL of acetic anhydride, and 250 mL of acetic acid was slowly added 14 mL of concentrated H_2SO_4, dropwise. The temperature of the reaction mixture was maintained between 10 and 20 °C with an ice bath. The mixture was stored overnight at room temperature and then was poured into 800 mL of ice. After the ice had melted the product was extracted with $CHCl_3$ (3 × 50 mL), and the combined $CHCl_3$ solution was washed with H_2O (2 × 100 mL), saturated $NaHCO_3$ solution (250 mL), and again with H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated, and traces of acetic acid were removed by coevaporation with toluene. A colorless syrup of **3** was obtained: 12.5 g (98% yield). The NMR spectrum showed that the isopropylidene singlet of **2** had been replaced with an acetyl peak at 2.07 ppm.

Five grams (12.9 mmol) of **3** was condensed with 6-(benzamidochloromercuri)purine as described in the previous publication on this subject.[5] The crude, blocked nucleoside was partially purified on a silicic acid column (55 × 4 cm, Mallinckrodt, 100 mesh) exactly as described in the prior case.[5] A foam (**4**, 3.5 g) was obtained, which had λ max (MeOH) 278 nm and gave a positive Beilstein test for halogen. A mixture containing 3 g of **4**, 1.2 g of DBU, and 30 mL of dry DMF was kept for 25 h at room temperature. The solvent was evaporated at 35° C (vacuum pump). The residue **5** was dissolved in 50 mL of MeOH and 50 mL of concentrated NH_4OH was added. After 25 h at room temperature, the solvents were removed by evaporation. The syrup was dissolved in a minimal amount of H_2O and placed on a column (35 × 2.5 cm) of Bio-Rad AG1-X2 (200–400 mesh, OH⁻)

ion-exchange resin. The column was eluted with H_2O and 15-mL fractions were collected. Fractions 3–20 and 25–60, the two major UV absorbing peaks, were pooled. The first peak was identified as benzamide[5] and the second peak afforded 1.2 g of crystalline **6** which was recrystallized from EtOH to give 0.9 g (32.5% yield from **3**): mp 195–196 °C; $[\alpha]^{23}_D$ −55.5° (*c* 0.7, MeOH); UV λ max (MeOH) 258 nm (ε 14 700); NMR (Me_2SO-d_6) δ 8.33, 8.16 (both s, 1 proton each, H-8, H-2), 7.32 (br s, 2, NH_2), 6.12 (d, 1, $J_{1',2'}$ = 2.8 Hz, H-1'), 6.02 (br s, 2, 2'-, and 3'-OH), 4.8–4.45 (m, 2, H-2', H-3'), 4.32, 4.20 (both br s, 1 proton each, H-5a', H-5b'). Anal. ($C_{10}H_{11}N_5O_3$) C, H, N.

1,2-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-arabinofuranose (10). A mixture containing 15 g (53 mmol) of (2,2,2-trichloroethyl)-α-D-arabinofuranoside[13] in 25 mL of dry pyridine was treated with 10.5 g (55 mmol) of *p*-toluenesulfonyl chloride in 50 mL of pyridine. The mixture was kept at room temperature for 32 h and evaporated under reduced pressure, and the residue was partitioned between 100 mL each of benzene and H_2O. The benzene layer was separated, washed with 10% HCl solution and water, and dried ($MgSO_4$). The benzene was removed by evaporation to give 25.4 g of syrupy (2,2,2-trichloroethyl)-5-*O*-*p*-toluenesulfonyl-α-D-arabinofuranoside. The latter was dissolved in 300 mL of acetone, and 30 g of $ZnCl_2$ and 25 g of activated Zn dust[21] were added. The stirring mixture was chilled in an ice bath and 7.5 mL of concentrated H_2SO_4 was added dropwise. The mixture was stirred at room temperature for 2 h and then treated with 50 mL of pyridine. The precipitate was removed by filtration and washed with acetone. The filtrate was evaporated, and the residue was partitioned between 100 mL of $CHCl_3$ and 500 mL of water that had been acidified with HCl. The $CHCl_3$ layer was dried ($MgSO_4$), and upon evaporation of the solvent a crystalline substance (5.8 g) separated, which was isolated by filtration and washed with $CHCl_3$. This substance had a melting point of 162–165 °C and gave a strong Beilstein test for halogen, but it did not appear to be a carbohydrate derivative based upon NMR data. No further work was done on this material. The filtrate and washings were combined and treated with Darco-G-60. The solvent was evaporated, the colorless syrup was dissolved in 20 mL of ethyl acetate, and ethyl ether was added until the mixture became turbid. Crystallization of **10** at 0 °C afforded 7.5 g (41% yield from **9**): mp 134–135 °C; $[\alpha]^{24}_D$ +34.8° (*c* 1, $CHCl_3$) [lit.[22] (for the L form) mp 129–130 °C; $[\alpha]^{24}_D$ −34.8° (*c* 2.026, $CHCl_3$); Kalvoda et al.[13] reported mp 127–130 °C for **10**]; NMR ($CDCl_3$) δ 7.83, 7.42 (both d, 4, protons of tosyl ring), 5.92 (d, 1, $J_{1,2}$ = 3.8 Hz, H-1), 4.72 (d, 1, $J_{1,2}$ = 3.8 Hz, H-2), 4.46 (s, 1, H-3), 4.36 (s, 3, H-4, H-5a, H-5b), 2.82 (br s, 1, 3-OH), 2.63 (s, 3, tosyl CH_3), 1.55, 1.47 (both s, 6, *gem*-dimethyl).

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-arabinofuranose (11). A solution containing 6 g (17.4 mmol) of **10** in 50 mL of 2-butanone was treated with 6 g (40 mmol) of NaI as described for the preparation of **2**. The workup was also identical and afforded a syrup which was dissolved in 20 mL of ethyl acetate. *n*-Hexane was added to incipient turbidity, and the flask was stored at 0 °C. The product **11** crystallized to afford 4.8 g (92% yield): mp 69–70 °C; $[\alpha]^{25}_D$ −7.1° (*c* 0.79, $CHCl_3$) [lit.[22] (for the L form) mp 66–67 °C; $[\alpha]^{27}_D$ +6.86° (*c* 2.04, $CHCl_3$)]; NMR ($CDCl_3$) δ 6.03 (d, 1, $J_{1,2}$ = 3.8 Hz, H-1), 4.64 (d, 1, $J_{1,2}$ = 3.8 Hz, H-2), 4.50 (br s, 1, H-3), 4.26 (br d, 1, H-4), 3.53, 3.40 (both s, 1 proton each, H-5a, H-5b), 2.73 (br s, 1, 3-OH), 1.60, 1.36 (both s, 6, *gem*-dimethyl). Anal. ($C_8H_{13}IO_4$) C, H.

9-(5-Deoxy-α-D-*threo*-pent-4-enofuranosyl)adenine (14). Acetolysis of **11** (2.5 g) was carried out as described for **2**, and 2.8 g (87% yield) of **12** was obtained as a syrup: NMR δ 2.14 (acetyl).

Compound **12** (2.5 g, 6.5 mmol) was converted to the blocked nucleoside **13** as described for the preparation of **4**. A foam weighing 2.1 g was obtained from the silicic acid column: λ max (MeOH) 278 nm and a positive Beilstein test. The remaining steps in the preparation of **14** were identical with those used to prepare nucleoside **6**. Crystals (0.68 g) were obtained after chromatography on the ion-exchange column. Recrystallization from EtOH gave 0.52 g (34% from **12**) of **14**: mp 194–195 °C; $[\alpha]^{23}_D$ + 54.2° (*c* 0.78, MeOH). The IR and NMR spectra of **14** were identical with that of **6**. Anal. ($C_{10}H_{11}N_5O_3$) C, H, N.

3,5-Dideoxy-5-iodo-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (16). A solution containing 2.8 g of **15**, 40 mL of 2-butanone, and 5 g of NaI was boiled under reflux for 24 h. Sodium *p*-toluenesulfonate was removed by filtration and the solvent was evaporated. The oil was dissolved in $CHCl_3$ (25 mL), washed with sodium thiosulfate solution (25 mL) and H_2O (3 × 25 mL), and dried ($MgSO_4$), and the $CHCl_3$ was evaporated to give a syrup that crystallized from ethyl acetate–*n*-hexane: yield 1.86 g (80%); mp 72–73 °C; $[\alpha]^{26}_D$ −8.6° (*c* 0.6, $CHCl_3$); NMR ($CDCl_3$) δ 6.06 (d, 1, $J_{1,2}$ = 4.2 Hz, H-1), 4.96 (t, 1, H-2), 4.33 (m, 1, H-4), 3.53, 3.44 (both s, 1 proton each, H-5a, H-5b), 2.66–1.86 (m, 2, H-3, H-3'), 1.66, 1.48 (both s, 6, *gem*-dimethyl). Anal. ($C_8H_{13}IO_3$) C, H.

9-(3,5-Dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine (19). From Route A. To a solution of **16** (1.6 g) in a mixture of acetic acid (50 mL) and acetic anhydride (5 mL) was added concentrated H_2SO_4 (3 mL) dropwise, while the flask was chilled in an ice bath. The flask was kept at room temperature overnight and then poured on ice chips (200 mL). After the ice melted the product was extracted with $CHCl_3$ (3 × 25 mL) and the combined $CHCl_3$ solution was washed with H_2O (2 × 50 mL), saturated $NaHCO_3$ (100 mL), and again with H_2O. After drying ($MgSO_4$), the $CHCl_3$ was evaporated and traces of acetic acid were removed by coevaporation of toluene. A colorless syrup (**17**) weighing 1.7 g (81%) was obtained. The NMR spectrum showed that the isopropylidene peak was gone and acetyl peaks at δ 2.12 and 2.08 were present.

The diacetate **17** was condensed with 6-(benzamidochloromercuri)purine and the blocked nucleoside **18** (0.72 g) was purified as previously described.[5] The nucleoside **18** was dissolved in 3 mL of DMF and treated with DBU (0.5 g). The removal of blocking groups and chromatographic isolation of the nucleoside were as described for the preparation of **6**. The product **19** (0.18 g, 15% from **17**) was crystallized from water: mp 165–167 °C (change in crystal structure), 230–235 °C (melted with decomposition); $[\alpha]^{27}_D$ −39.9° (*c* 0.71, H_2O); UV λ max (H_2O) 259 nm (ε 14 750); NMR (Me_2SO-d_6) δ 8.46, 8.26 (both s, 1 proton each, H-8, H-2), 7.40 (br s, 2, NH_2), 6.08 (d, 1, $J_{1',2'}$ = 1.2 Hz, H-1'), 5.23 (d, 1, H-2'), 5.08 (br s, 1, 2'-OH), 4.5–4.18 (2, H-5a', H-5b'), 2.92–2.64 (m, 2, H-3a', H-3b'). Anal. ($C_{10}H_{11}N_5O_2 \cdot H_2O$) C, H, N.

From Route B. Acetolysis of 1.7 g of **24** was carried out as described for **16** to give 1.8 g (91%) of the diacetate **25**. Condensation of **25** (1.6 g) with the base was performed as described above and the fully blocked syrupy nucleoside **26** was obtained from chromatography on a column of silicic acid. During the latter procedure another fast-moving product was obtained as a syrup (0.15 g). This substance gave a positive Beilstein test but had no purine. Elemental analysis and the NMR spectrum indicated that it was the disaccharide **27**: $[\alpha]^{27}_D$ −15.8° (*c* 3.1, $CHCl_3$); NMR ($CDCl_3$) δ 5.60, 5.52 (s, 1.7, H-1, H-1', β anomers, and s, 0.3, H-1, α anomer), 5.15, 5.06 (both d, 1 proton each, $J_{2,3}$ = 1.5 Hz, H-2, H-2'), 4.56 (m, 2, H-4, H-4'), 4.09 (m, 2, H-5a, H-5b), 3.35, 3.26 (both s, 2, H-5a', H-5b'), 2.74–2.43 (m, 4, H-3a, H-3b, H-3a', H-3b'), 2.2 (s, 3, OAc), 2.17 (s, 6, 2-OAc, 2'-OAc). Anal. ($C_{16}H_{23}O_9I$) C, H.

The remaining steps in the preparation of **19** were identical with those of the conversion of **18** to **19** and afforded 0.13 g (11.5%) after recrystallization. The melting point, optical rotation, and IR and NMR spectra were identical with the product obtained from route A.

3-Deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-L-*threo*-pentofuranose (23). 3-Deoxy-1,2-*O*-isopropylidene-β-L-*threo*-pentodialdofuranose[10] (**21**; 3 g) was reduced with Raney nickel in EtOH under reflux and chromatographed on silicic acid (9:1 $CHCl_3$–acetone) to afford **22** (2.4 g, 80%): $[\alpha]^{27}_D$ −14.2° (*c* 0.8, EtOH); NMR ($CDCl_3$) δ 5.83 (d, 1, $J_{1,2}$ = 4.2 Hz, H-1), 4.77 (m, 1, H-2), 4.27 (m, 1, H-4), 3.73 (m, 2, H-5a, H-5b), 2.83 (br s, 1, 5 OH), 2.32–2.06 (m, 2, H-3a, H-3b), 1.57, 1.33 (both s, 6, *gem*-dimethyl).

Compound **22** (2.4 g) was treated with *p*-toluenesulfonyl chloride (2.6 g) in dry pyridine in the usual fashion. Upon pouring the mixture over ice chips (150 mL), the product crystallized, affording 3.6 g (80%). Recrystallization of **23** from EtOH gave fine needles: mp 76–77°C; $[\alpha]^{27}_D$ −48.8° (*c* 0.7, $CHCl_3$); NMR ($CDCl_3$) δ 7.84, 7.34 (both d, 4, aromatic ring), 5.80 (d, 1, $J_{1,2}$ =

3.6 Hz, H-1), 4.7 (q, 1, H-2), 4.24 (m, 3, H-4, H-5a, H-5b), 2.46 (s, 3, tosyl CH_3), 2.12 (q, 2, H-3a, H-3b), 1.37, 1.27 (both s, 6, *gem*-dimethyl). Anal. ($C_{15}H_{20}O_6S$) C, H, S.

3,5-Dideoxy-5-iodo-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (24). A solution of **23** (2.5 g), 2-butanone (50 mL), and NaI (5 g) was boiled under reflux for 24 h. The same workup as previously described afforded a clear oil that crystallized from cold ethyl acetate–*n*-hexane as needles but melted at room temperature: $[\alpha]^{25}_D$ -14.1° (*c* 2.3, $CHCl_3$); NMR ($CDCl_3$) δ 5.86 (d, 1, $J_{1,2}$ = 3.6 Hz, H-1), 4.76 (q, 1, H-2), 4.4 (m, 1, H-4), 3.53, 3.40 (both s, 2, H-5a, H-5b), 2.3 (m, 2, H-3a, H-3b), 1.56, 1.33 (both s, 6, *gem*-dimethyl). Anal. Calcd for $C_8H_{13}IO_3$: C, 33.82; H, 4.61. Found: C, 33.35; H, 4.50.

Polarimetric Studies. The procedure used for the periodate oxidation and borohydride reduction has been reported previously.[12,23] 9-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**8**) was the reference and was oxidized for 18 h. Because of trans hydroxyl groups, nucleoside **6** was oxidized for 5 days. The final solution of dialcohol **7** derived from **6** had $[\alpha]_D$ +59°, whereas the solution derived from **8** had $[\alpha]_D$ +55°.

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Antileukemic Activity of Substituted Ureidothiazoles, Ureidothiadiazoles, and Related Compounds

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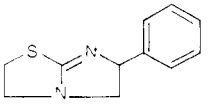
A number of ureidothiazole and ureidothiadiazole derivatives related to ethyl 4-[[(2-thiazolylamino)carbonyl]-amino]benzoate were prepared and evaluated against the leukemia P-388 tumor system in mice. Preliminary structure activity relationship study revealed that, among other considerations, active compounds of this series contain either an "isothioureido" [>N–C(S–)=N–] or an "isothiosemicarbazono" [>N–C(S–)=N–N=] structural unit.

A comparison of the structures of a number of nitrogen- and sulfur-containing heterocyclic compounds possessing antineoplastic activity reveals a definite structural arrangement of certain key atoms. Levamisole[1] (**1**) was



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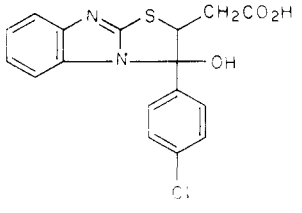

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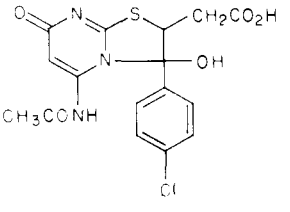

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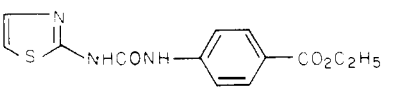
reported to have antitumor activity against Lewis lung carcinoma,[2] rhabdomyosarcoma,[3] other experimental systems,[4] and man.[5] This drug acts as a nonspecific stimulant of the immune system.[6] Levamisole and its analogues are inhibitors of alkaline phosphatase.[6] A fused benzimidazolylthiazoleacetic acid derivative **2** and a pyrimidylthiazoleacetic acid derivative **3** were also known to be active against Lewis lung tumor.[7]

Recently, a ureidothiazole derivative **4** (Carbolabs, Inc.)



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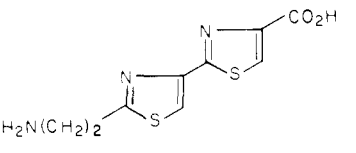

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was found to possess interesting biological activity.

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