by general procedure B from 17: yield, melting point, etc. are shown in Table IV; IR (KBr pellet) 3380 and 3200 (NH_2), 1705 (S-acetyl C=O), 1670 (lactam C=O), 1635 cm^{-1} (amide C=O). Anal. ($C_{10}H_{16}N_2O_3S$) C, H, N.

3-(Mercaptomethyl)-2-oxo-1-piperidineacetamide (19). This compound was prepared by general procedure C from 18: yield, melting point, etc. are shown in Table IV; IR (KBr pellet) 3360 and 3180 (NH_2), 2540 (SH), 1665 (lactam C=O), 1630 cm^{-1} (amide C=O). Anal. ($C_8H_{14}N_2O_2S$) C, H, N.

Pharmacology Methods. Assay for in Vitro Angiotensin-Converting Enzyme Inhibitory Activity. ACE inhibitory activity was determined by means of a commercial kit for the radioassay of ACE activity (Ventrex Laboratories; Portland, Maine). In this assay, ACE inhibitory activity was determined by using unpurified guinea pig serum ACE in the presence and absence of the test compound. ACE from guinea pig serum and the test compounds were preincubated for 10 min before the addition of the labeled substrate [^{3}H]hippurylglycylglycine. After a 60-min incubation at 37 °C, the reaction was stopped by the addition of 0.1 N hydrochloric acid. ACE cleaves the hippuryl-glycyl bond to form the dipeptide glycylglycine and [^{3}H]-hippuric acid. The [^{3}H]hippuric acid was then extracted with ethyl acetate, and the ACE of a given sample was calculated as the amount of [^{3}H]hippuric acid generated. Activity is reported as the IC_{50}, which is the approximate molar concentration of test compound causing a 50% inhibition of the control converting-enzyme activity.

Guinea Pig Ileum Assay. Compounds were evaluated for their effects on contractile responses of guinea pig ileum to angiotensin I (AI; 2×10^{-8} M), angiotensin II (AII; 2×10^{-8} M), bradykinin (BK; 10^{-8} M), and carbachol (10^{-7} M). In this test, 3- to 5-cm segments of ileum from female guinea pigs were mounted in 50-mL baths containing aerated Tyrode's solution with a resting force of 0.2–0.5 g at 37 °C. The contractile responses were recorded via force-displacement transducers (FT .03C; Grass Instrument, Quincy, Mass.) and a strip chart recorder (Model 260; Gould-Brush, Cleveland, Ohio). Test drugs were added to the bath 2 min prior to the agonist. In a given experiment, four tissues were exposed to only one agonist and one antagonist. Activity was expressed as the approximate molar concentration producing 50% inhibition (IC_{50}) of AI, AII, or carbachol or a 50% potentiation (PC_{50}) of the bradykinin response.

Oral and Intravenous ACE Inhibitory Activity in a Concious Normotensive Dog. In these experiments, inhibition of the blood-pressure response to reproducible submaximal iv doses of AI was used as an index of ACE inhibition. Dogs were prepared for blood-pressure monitoring and iv drug injection by implantation of a silastic catheter in the left femoral artery and vein, respectively. The arterial catheter was connected to a pressure transducer (P23AA; Statham; Hato Rey, Puerto Rico), and blood pressure and heart rate were recorded on a strip chart recorder (Type RM dynograph, Beckman Instruments, Schiller Park, Ill). All experiments were performed in a single dog over a period of 6 days.

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Synthesis and Antiviral Activity of 1-(2-Deoxy-β-D-ribofuranosyl)-5-(methylmercapto)-2-pyrimidinone

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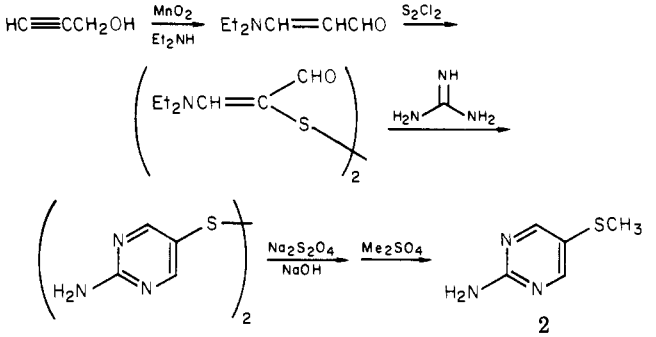
1-(2-Deoxy-β-D-ribofuranosyl)-5-(methylmercapto)-2-pyrimidinone (1b) was synthesized via modification of the silyl method. 1b inhibits the Herpes simplex virus type 1 (98%) and type 2 (97%) at a concentration which is nontoxic to human HeLa cells. The compound shows 50 times greater binding affinity (lower K_i) to the virus-specific thymidine kinase than to the thymidine kinase of uninfected HeLa cells.

A variety of 5-substituted 2′-deoxyuridine analogues have shown antiherpes activity. These include compounds where the 5-substituent is halogen, alkyl, vinyl, ethynyl, hydroxymethyl, or thiocyanato.[1] 5-(Methylmercapto)-2′-deoxyuridine, previously synthesized in this laboratory,[2] was also shown to be an inhibitor of herpes simplex type 1 virus (HSV-1).[3] We are currently studying 5-substituted 2-pyrimidinone nucleoside analogues. 2-Pyrimidinones may be considered to be uracil analogues lacking the N-3 hydrogen and the C-4 oxygen. Several nucleoside derivatives of 2-pyrimidinones have shown biological activity. 5-Fluoro-2-pyrimidinone deoxyriboside inhibited DNA synthesis in *Escherichia coli*, whereas the corresponding 2-pyrimidinone deoxyriboside was inactive.[4] 2-Pyrimidinone β-D-ribofuranoside was reported to inhibit the growth of *E. coli*[5] and vaccinia virus.[6] 1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-2-pyrimidinone 5′-phosphate and the corresponding 5-methyl-2-pyrimidinone nucleotide

Scheme I



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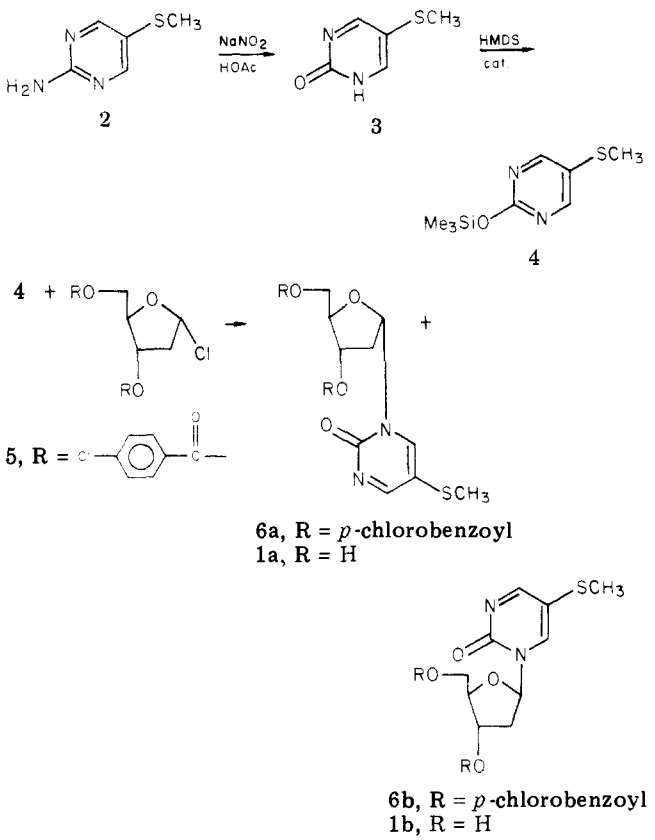
Scheme II



were shown to be good inhibitors of thymidylate synthetase.[5]

During research directed toward the synthesis of a variety of novel 5-substituted 2-pyrimidinone nucleosides, the title compound, 1-(2-deoxy-β-D-ribofuranosyl)-5-(methylmercapto)-2-pyrimidinone (**1b**) was prepared and found to have interesting antiherpes activity.

Chemistry. Oxidation of propargyl alcohol with active manganese dioxide in the presence of diethylamine gave β-(diethylamino)acrolein,[7] which was converted to 2-amino-5-(methylmercapto)pyrimidine (**2**) in four steps according to the method of Gompper et al.,[8] with minor modification[9] (Scheme I). Compound **2** underwent diazotization and subsequent hydrolysis with aqueous acetic acid–sodium nitrite to give 5-(methylmercapto)-2-pyrimidinone (**3**) (Scheme II). Compound **3** was trimethylsilylated to **4** using 1,1,1,3,3,3-hexamethyldisilazane and condensed with the protected chlorosugar **5**[2] (Scheme II) by two different methods. The first procedure, involving condensation in dry benzene in the presence of 4Å molecular sieves, has been shown in the synthesis of a 6-methylcytosine nucleoside to increase the amount of β anomer relative to the α anomer in the product.[10] This procedure under the conditions used here gave a 54% yield of the α-anomer **6a** and a 13% yield of the β-anomer **6b** after fractional crystallization from ethanol. An alternative method involving fusion in vacuo of the appropriately protected chloro sugar and a silylated pyrimidine was reported to yield β anomers as the predominant product when various silylated 5-thiouracils were used.[2] In this case, this procedure gave a yield of 36% of **6a** and 8.6% of **6b** after separation of the anomers by fractional crystallization. Thus, in both syntheses, the α/β ratio of the isolated compounds was about 4:1. The nucleosides **6a** and **6b** were deblocked with anhydrous ammonia in methanol to give **1a** and **1b**, respectively. The assignment of anomeric configuration was made by the NMR spectra[11] of **1a** and **1b**: the α-anomer **1a** showed the anomeric proton signal as an apparent quartet of peak width 9 Hz. The anomeric proton of the β-anomer **1b** appeared as an apparent triplet of peak width 12 Hz.

Table I. Anti-Herpes Simplex Virus Activity of 1-(2-Deoxy-β-D-ribofuranosyl)-5-(methylmercapto)-2-pyrimidinone (1b)

	plaque-forming units/mL[a]	
concn, μM	HSV-1 (KOS)	HSV-2 (333)
	1.5×10^7	1.2×10^7
100	6.4×10^6	1.3×10^7
200	1.7×10^6	3.1×10^6
400	3.4×10^5	3.2×10^5
25[b]	1.0×10^5	5.0×10^5

[a] See Experimental Section. [b] 5-Propyl-2′-deoxyuridine[12] used as a standard.

Table II. Binding Affinity of 1-(2-Deoxy-β-D-ribofuranosyl)-5-(methylmercapto)-2-pyrimidinone (1b) to Thymidine Kinase from Various Sources

source of thymidine kinase	K_i, μM
HeLa cytosol	>400[a]
HeLa mitochondria	160
HSV-1-infected Hela Bu	2.0
Varicella zoster virus infected human cells	4.1

[a] No inhibition of the phosphorylation of [^{14}C]thymidine (25 μM) was observed in the presence of 400 μM compound.

Biological Activity. Compound **1b** was examined for its anti-HSV-1 (KOS strain) and anti-HSV-2 (333 strain) activity with the procedures described previously.[12] The results are presented in Table I. At a concentration of 400 μM, a 98% reduction of HSV-1 titer and a 97% reduction of HSV-2 titer were observed. The HSV-1 mutant (B 2006 strain), which lacks the ability to induce virus-specific thymidine kinase (TK) in infected cells, could not be inhibited by this compound at the concentration of 400 μM. Thus, virus-specific TK is required for its antiviral effects. Compound **1b** could also inhibit the growth of human HeLa cells in culture; the concentration needed to inhibit 50% of cell growth was found to be 1 mM. The preferential anti-HSV activity of **1b** over its anti-cell-growth activity seems to be related to its preferential binding affinity to virus-specific TK over that of human cytosol and mitochondrial TK as shown in Table II. Varicella zoster virus (VZV) specific TK was also included for comparison. On the basis of the binding affinity of compound **1b** to VZV TK, it is anticipated that this compound may also have anti-VZV activity. The lack of oxygen at position 4 of the base could render this compound resistant to the action of thymidine phosphorylase which can inactivate several biologically active thymidine or

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deoxyuridine analogues such as the 5-iodo-, 5-(trifluoromethyl)- and 5-(fluoropropyl)-2′-deoxyuridines. This could be advantageous if compounds such as **1b** are used in vivo.[13] Further synthetic and biochemical investigations to exploit this new lead are in progress.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were obtained on a Beckman DB-G spectrophotometer. NMR spectra were recorded on Varian A-60 and T-60 spectrometers and δ values are reported downfield from the tetramethylsilane internal standard unless otherwise indicated. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., or by Galbraith Laboratories, Inc., Knoxville, Tenn. Optical rotations were measured on a Perkin-Elmer 141 polarimeter using a wavelength of 589 nm (sodium lamp). Thin-layer chromatography was performed on microscope slides with silica gel HF-254, and components were visualized by iodine vapor or ultraviolet light. Preparative thin-layer chromatography was done using 20 × 20 cm plates coated with approximately 20 g of silica gel PF-254 (EM 7747) per plate. Solutions were concentrated by rotary evaporation under aspirator vacuum.

5-(Methylmercapto)-2-pyrimidinone (3). 2-Amino-5-(methylmercapto)pyrimidine (**2**; 3.40 g, 24.1 mmol) was dissolved in 40 mL of HOAc–H_2O (70%, v/v) and heated on a 60–65 °C bath. Sodium nitrite (4.99 g, 72.3 mmol) was added in portions over 35 min. Heating was continued for another 2 h, and then the solution was cooled and concentrated to a paste. The paste was redissolved in 80 mL of water, and the solution was again concentrated. Water (5 mL) was added, and the mixture was cooled on ice and filtered to give 2.35 g (16.5 mmol, 69%) of **3** as yellow crystals. Recrystallization from EtOH gave 1.79 g (12.6 mmol, 52%) of yellow crystals of **3**: mp 198.5–200 °C; UV (EtOH) λ_{max} 252 nm (sh, ϵ 8060), 321 (1870); NMR (Me_2SO-d_6) δ 2.38 (s, 3, SCH_3), 8.37 (s, 2, C_4 H and C_6 H). Anal. ($C_5H_6N_2OS$) C, H, N, S.

1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl]-5-(methylmercapto)-2-pyrimidinone (6a). A. A mixture of 5-(methylmercapto)-2-pyrimidinone (**3**; 0.900 g, 6.34 mmol), 1,1,1,3,3,3-hexamethyldisilazane (HMDS; 12.2 mL), and trimethylchlorosilane (0.1 mL) was stirred on a 95–100 °C oil bath, with protection from moisture, until the mixture was homogeneous (2 h). After cooling to room temperature, the solution was coevaporated twice with dry toluene (50 mL) to a syrup (max 40 °C), which was then dissolved in dry benzene (150 mL) and 4Å molecular sieves (19 g, Davison, 14–30 mesh) were added with 1-chloro-2-deoxy-3,5-bis-*O*-(*p*-chlorobenzoyl)-D-ribofuranose[2] (**5**; 3.71 g, 8.63 mmol). This mixture was stirred in the dark at room temperature for 2 days, protected from moisture. The reaction mixture was filtered into absolute MeOH (40 mL), and the sieves were washed twice with dry benzene. The combined filtrate and washings were concentrated to a syrup (max 30 °C), which was completely dissolved in $CHCl_3$ (25 mL) and concentrated to a yellow syrup–foam (4.296 g).

This crude product was dissolved in $CHCl_3$ (30–40 mL), evaporated onto dry column silica gel (20 g, ICN 04526), placed on top of a silica gel dry column (500 g, 45 mm × 21 in.), and developed with $CHCl_3$–EtOAc (5:2, 560 mL). The large fluorescent band under UV light was cut out and eluted with $CHCl_3$, EtOAc, and EtOH. The combined eluents were concentrated, dissolved in $CHCl_3$ (45 mL), filtered through Celite filter aid, and concentrated to a white solid, yielding 3.20 g (5.98 mmol, 94% of **6a** and **6b** mixture). This solid was dissolved in boiling absolute EtOH (110 mL) and allowed to cool slowly to give 1.83 g (3.42 mmol, 54%) of the α-anomer **6a** as white crystals: mp 184–185 °C; $[\alpha]^{25}_D$ -9.4° ($CHCl_3$, *c* 1.0); NMR ($CDCl_3$) δ 2.23 (s, 3, SCH_3), 2.90 (m, 2, C_2' H), 4.57 (m, 2, C_5' H), 5.00 (m, 1, C_4' H), 5.60 (apparent d, 1, C_3' H, J = 5 Hz), 6.25 (apparent d, 1, C_1' H, J = 5 Hz), 7.27–8.15 (m, 9, aromatic H and C_4 H), 8.65 (br s, 1, C_6 H). This product was recrystallized from absolute EtOH to give an analytically pure sample of **6a**: mp 186–186.5 °C; $[\alpha]^{25}_D$ -10.2° ($CHCl_3$, *c* 1.05); UV ($CHCl_3$) λ_{max} 324 nm (ϵ 2580), 283 (2620). Anal. ($C_{24}H_{20}Cl_2N_2O_6S$) C, H, Cl, N, S.

B. A mixture of **3** (0.872 g, 6.14 mmol), HMDS (10 mL), and a few milligrams of ammonium sulfate was stirred at 100 °C with protection from moisture for ca. 3 h. After the mixture cooled to room temperature, excess HMDS was removed in vacuo and the residue was coevaporated with dry toluene (20 mL). To the residue was added the chloro sugar **5** (2.66 g, 6.20 mmol), and the mixture was fused at 105–110 °C under aspirator vacuum for 12 min. Chloroform (25 mL) was added after cooling, followed by absolute EtOH (1 mL). After awhile this was concentrated, additional $CHCl_3$ (25 mL) was added, and the yellow solid was filtered off to give a 21% recovery (185 mg) of **3**. The combined filtrate and $CHCl_3$ washings were purified by silica gel dry column chromatography as in method A. EtOAc eluent of the product band of the column was concentrated at room temperature to give a light yellow solid (2.15 g, 4.02 mmol, 65% of **6a** and **6b** mixture), which was recrystallized from absolute EtOH (75 mL) to give 1.18 g (2.20 mmol, 36%) of the α-anomer **6a** as white crystals: mp 179–181 °C; $[\alpha]^{26}_D$ -10.4° ($CHCl_3$, *c* 1.07).

1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl]-5-(methylmercapto)-2-pyrimidinone (6b). A. The mother liquor of the crude α-anomer **6a** (method A) was concentrated to a gum, redissolved in a small amount of boiling absolute EtOH, and cooled slowly to give 0.439 g (0.820 mmol, 13%) of an off-white solid of crude β-anomer **6b**: mp 155–162 °C; $[\alpha]^{25}_D$ +5.7° ($CHCl_3$, *c* 0.89). This product (0.419 g) was recrystallized from absolute EtOH (15 mL) to yield 0.297 g (0.555 mmol, 8.8%) of **6b** as an off-white solid: mp 174–176 °C; $[\alpha]^{25}_D$ +5.1° ($CHCl_3$, *c* 0.925); NMR ($CDCl_3$) δ 2.22 (s, 3, SCH_3), 4.70 (m, 3, C_4' H and C_5' H), 5.58 (apparent d, 1, C_3' H, J = 7 Hz), 6.22 (apparent q, 1, C_1' H, J = 9 and 6.5 Hz, peak width 15 Hz), 7.28–8.15 (m, 9, aromatic H and C_4 H), 8.55 (m, 1, C_6 H); UV ($CHCl_3$) λ_{max} 327 nm (ϵ 2980), 281 (3150). Anal. ($C_{24}H_{20}Cl_2N_2O_6S$) C, H, Cl, N, S.

B. The mother liquor of the crude α-anomer **6a** (method B) was concentrated to a gum, dissolved in boiling absolute EtOH (15 mL), and allowed to cool to room temperature overnight. It was then cooled for 1 h at 5 °C and filtered, and the product was washed with EtOH to yield a slightly yellow solid (0.600 g). This was recrystallized from EtOH (20 mL) and seeded to give 0.282 g (0.527 mmol, 8.6%) of β-anomer **6b** as slightly yellow crystals. An additional crystallization from EtOH (10 mL) afforded white crystals of **6b** (0.208 g): mp 170–171 °C; $[\alpha]^{26}_D$ +5.4° ($CHCl_3$, *c* 0.76).

1-(2-Deoxy-α-D-ribofuranosyl)-5-(methylmercapto)-2-pyrimidinone (1a). Compound **6a** (0.612 g, 1.14 mmol) was added to dry MeOH (60 mL) saturated with anhydrous ammonia at 0 °C. The mixture was stirred at 0 °C until **6a** completely dissolved (30 min) and was then kept at 0–1 °C for 3 days. The solvent was evaporated and the residue was partitioned between $CHCl_3$ and H_2O. Evaporation of the water layer at room temperature yielded a yellow syrup (0.360 g), which was purified on two silica gel preparative TLC plates (20 × 20 cm), developing with EtOAc–EtOH (5:1). Elution of the main band with EtOH and MeOH and concentration of the combined eluents yielded 0.280 g (1.08 mmol, 95%) of the thick syrup of **1a**. A gummy material was obtained upon attempted precipitation of **1a** from EtOH with Et_2O: TLC (EtOAc–EtOH, 5:1) R_f 0.47; NMR (D_2O, external Me_4Si) δ 2.40 (s, 3, SCH_3), 3.69 (d, 2, C_5' H, J = 5 Hz), 4.53 (m, 2, C_3' H and C_4' H), 6.10 (dd, 1, C_1' H, J = 7 and 2 Hz, peak width 9 Hz), 8.23 (apparent t, 1, C_4 H, J = 4 Hz), 8.48 (m, 1, C_6 H); $[\alpha]^{26}_D$ -54.4° (H_2O, *c* 1.12); UV (H_2O) λ_{max} 250 nm (sh, ϵ 7130), 324 (2410). Anal. ($C_{10}H_{14}N_2O_4S \cdot H_2O$) C, H, N, S.

1-(2-Deoxy-β-D-ribofuranosyl)-5-(methylmercapto)-2-pyrimidinone (1b). Compound **6b** (0.474 g, 0.885 mmol) was added to dry MeOH (60 mL) saturated with anhydrous ammonia at 0 °C and stirred at 0–5 °C for 5 days. The workup and purification were the same as for compound **6a**, yielding 0.239 g (0.866 mmol, 98% as the monohydrate) of a slightly yellow syrup of **1b**: TLC (EtOAc–EtOH, 5:1) R_f 0.61; NMR (D_2O, external Me_4Si) δ 2.33 (s, 3, SCH_3), 3.47–4.47 (m, 4, C_3' H, C_4' H, and C_5' H), 6.05 (t, 1, C_1' H, J = 6 Hz, peak width 12 Hz), 8.50 (s, 2, C_4 H and C_6 H); $[\alpha]^{26}_D$ +42.3° (H_2O, *c* 0.567). Compound **1b** gradually solidified

(13) Preliminary studies indicated that a relatively crude enzyme preparation from human liver containing both thymidine and uridine phosphorylases indeed failed to utilize compound **1b** as a substrate.

in the freezer: it was repurified on silica gel preparative plates and crystallized from EtOH-Et_2O: mp 112-114 °C; UV (H_2O) λ_{max} 253.5 nm (ϵ 7550), 321 (2340). Anal. ($C_{10}H_{14}N_2O_4S$) H, S, N; C: calcd, 46.50; found, 45.97.

Biological Assay Procedures. HeLa Bu cells were infected with HSV-1 or HSV-2 virus at a multiplicity of 5-10 plaque-forming units per cell. After 1-h virus adsorption, the drugs were added at 0-h postinfection. Virus titer of 24-h postinfected cultures was examined according to the previously described procedure.[12]

Thymidine kinase from various sources (see Table II) was purified by previously published procedures.[14-16] No contamination of thymidine phosphorylase and nucleoside monophosphate phosphotransferase was present in our preparations. The apparent K_i was determined by the method of Cheng and Prusoff.[17]

Acknowledgment. This work was supported by Grants 5-RO1-CA 06695-17 and 5-T32-CA 09166 from the National Cancer Institute, NIH, and CH-29C from the American Cancer Society.

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Synthesis of 2′-Deoxy-L-fucopyranosylcarminomycinone and -ϵ-pyrromycinone As Well As 2′-Deoxy-D-*erythro*-pentopyranosyldaunomycinone, -carminomycinone, and -ϵ-pyrromycinone

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Treatment of di-*O*-acetyl-2-deoxy-L-fucopyranosyl bromide with carminomycinone and ϵ-pyrromycinone in the presence of mercuric bromide and mercuric cyanide afforded 3′,4′-di-*O*-acetyl-2′-deoxy-L-fucopyranosylcarminomycinone and -ϵ-pyrromycinone. Similarly, when di-*O*-acetyl-2-deoxy-D-*erytrho*-pentopyranosyl chloride was treated with daunomycinone, carminomycinone and ϵ-pyrromycinone, the di-*O*-acetyl derivatives of the anthracyclinone glycosides were obtained. Deacetylation of the previous acetates with sodium methoxide afforded 2′-deoxy-L-fucopyranosylcarminomycinone and -ϵ-pyrromycinone, as well as 2′-deoxy-D-*erythro*-pentopyranosyldaunomycinone, -carminomycinone, and -ϵ-pyrromycinone. 2′-Deoxy-L-fucopyranosylcarminomycinone was found to be more active than carminomycin at higher dosages on L1210.

The anthracyclines form a group of antibiotics that comprises a number of antineoplastic agents used clinically, such as doxorubicin (adriamycin), daunorubicin, and carminomycin.[1] These antibiotics possess a substituted tetrahydronaphthacenedione ring system linked by a glycosidic linkage to the amino sugar daunosamine.[2,3]

Although the anthracyclines have shown remarkable antitumor activity with a T/C on P388 of 200 or more, their success clinically has been limited because of their cardiotoxicity,[3-7] which necessitates the stoppage of treatment before complete remission is established to prevent irreversible damage to the heart tissues. To suppress this untoward effect, modifications of the anthracycline molecule have been made in both the aglycon and the sugar moiety.[8-28]

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