decrease in the overall intensity of the uv maximum at 285 nm. A similar crude preparation containing the 4,6-dienone was obtained by boiling the compound in *tert*-BuOH with an equal weight of chloranil.

17α-Hydroxy-12α-etiojerva-4,6-dien-3-one (2b). **a. Oxidation** of the Enol Ether 4b. The unsaturated ketone 1b (1 g) was treated with dimethoxypropane according to procedure A and yielded an amorphous enol ether (1.0 g). This material was treated with DCDCQ in Me_2CO (procedure B), affording, by direct crystallization from Et_2O, 0.46 g of dienone 2b: mp 133–139°; ir 3680, 1660 cm^{-1}; uv 286 nm (ε 27,000); nmr 59 and 66 (18-Me), 66 (19-Me), 345 (4-H), 370 (6-H), 378 Hz (7-H). *Anal.* ($C_{19}H_{26}O_2$) C, H.

b. **Saponification of the Acetate 2e.** A solution of 0.20 g of the dienone 2e was stirred in 20 ml of *tert*-BuOH and 3 ml of 10% aqueous KOH for 18 hr. The solution was diluted with H_2O and extracted with Et_2O. The resulting product was chromatographed quickly and yielded, by elution with 20% EtOAc–C_6H_6, 75 mg of the dienone 2b, identical with that produced above.

12α-Etiojerva-4,6-diene-3,17-dione (2c). A solution of 0.11 g of the alcohol 2b in 10 ml of pyridine was oxidized with the Sarett reagent[8] prepared from 0.5 g of CrO_3 at room temperature. The product was isolated by ether extraction and was crystallized from aqueous Me_2CO to yield 35 mg of the diketone as a hemihydrate: mp 180–183°; ir 1720, 1750 cm^{-1}; uv 284 nm (ε 24,100); [α]D −33°. *Anal.* ($C_{19}H_{24}O_2 \cdot H_2O$) C, H.

7α-Thioacetyl-17α-acetoxy-12α-etiojerv-4-en-3-one (5e). The acetate 2d was allowed to stand in 1 ml of AcSH at room temperature for 24 hr. The solvent was removed under vacuum and the product was chromatographed quickly on a short bed of silica gel. The material eluted with 10% EtOAc–C_6H_6 crystallized from Et_2O and was recrystallized from Et_2O–hexane to yield 80 mg of the pure adduct 5e: mp 152–155°; ir 1730, 1700, 1670 cm^{-1}; uv 237 nm (ε 14,700); nmr 53 and 59 (18-Me), 71 (19-Me), 123 (OAc), 142 (SAc), 343 Hz (4-H). *Anal.* ($C_{23}H_{32}O_4S$) C, H.

7α-Acetylthio-17α-hydroxy-12α-etiojerv-4-en-3-one (5b). The dienone 2b (0.40 g) was allowed to stand in 1 ml of AcSH for 2 hr. The solvent was removed from Et_2O to give 0.25 g of the adduct 5b: mp 104–107°; ir 3680, 1710 cm^{-1}; uv 238 nm (ε 17,500); nmr 59 and 66 (18-Me), 71 (19-Me), 142 (SAc), 347 Hz (4-H). *Anal.* ($C_{21}H_{30}O_3S$) C, H; C: calcd, 69.58; found, 69.13; H: calcd, 8.34; found, 8.80.

7α-Acetylthio-12α-etiojerv-4-ene-3,17-dione (5c). A solution of 0.20 g of the alcohol 5b in 5 ml of Me_2CO was oxidized with 0.2 ml of 4 *N* CrO_3 (Jones reagent)[9] at 5°. After 10 min the solution was diluted with H_2O and the resulting precipitate was separated. Recrystallization from aqueous Me_2CO gave 120 mg of the ketone 5c: ir 1710, 1692, 1679 cm^{-1}; uv 238 nm (ε 16,100); nmr 57 and 63 (18-Me), 68 (19-Me), 142 (SAc), 347 Hz (4-H). *Anal.* ($C_{21}H_{28}O_3S$) C, H. Oxidation of the 17β-alcohol 5a proceeded in an analogous fashion to provide the same ketone 5c.

Allylic Bromination of 17β-Acetoxy-12α-etiojerva-1,4-dien-3-one (3d). The 1,4-diene 3d was treated with an equal weight of NBS in refluxing CCl_4. The resulting bromide on dehydrobromination with MgO gave dark mixtures containing no visible 1,4,6-trienone by spectral analysis (uv, nmr). An attempt to prepare the 1,4,6-trienone from the 4,6-diene 2a by use of DCDCQ in refluxing C_6H_6 for 20 hr afforded a dark oil containing some starting material but no discernible trienone (uv, nmr analysis).

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Synthesis of Nucleoside 5′-Carbamates†

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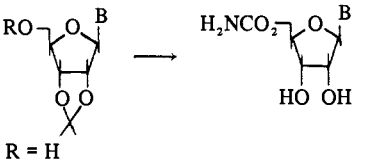
One of the difficulties encountered in the use of nucleosides in chemotherapy is that the nucleoside often requires conversion *in vivo* to a nucleotide for activation. Drug resistance then develops when the cells fail to perform this conversion.[1,2] Direct use of the nucleotide generally fails, presumably due to either enzymatic cleavage or failure of the highly charged molecules to cross the cell membrane. Several workers have tried, with varying degrees of success, to overcome this problem by substituting polar but nonionized groups for the 5′-phosphate.[1-6] Baker and coworkers, working *in vitro* with isolated enzyme systems, found evidence for simulation of phosphate by *O*-carbamate in a derivative of 6-mercaptopurine[3] but were unable to detect it with two other nucleoside-derived carbamates.[5] Because of the above theoretical considerations and Baker's partial success *in vitro*, as well as the occurrence of the *O*-carbamyl moiety in a variety of antitumor substances (*e.g.*, mitomycin,[7] bleomycin,[8] the acetylenic diarylcarbinol carbamates[9,10]), we were stimulated to prepare 5′-*O*-carbamyl nucleosides for *in vivo* antineoplastic evaluation as part of our continuing studies in the area of fraudulent nucleosides.

The nucleoside 5′-*O*-carbamates were prepared by the route shown in Scheme I, essentially that of Baker, *et al.*[5]

Scheme I



a, R = H
b, R = CO_2Ph
c, R = $CONH_2$

Yields in the final step (removal of the isopropylidine blocking group) were substantially improved by the use of 90% trifluoroacetic acid.[11] Intermediates in the preparation of the 6-methylthiopurine nucleoside 7 could not be isolated pure and would not crystallize. An attempt to apply this sequence to 2′,3′-isopropylidene adenosine resulted in a mixture of products at the phenylchloroformylation stage.

Intermediate 4 (see Table I) was not obtained pure and therefore was not submitted for antitumor screening. The other compounds were inactive against leukemia L-1210 in mice treated on days 1–5 with doses of 200 mg/kg/day in standard NCI assays.‡ In addition, compounds 1, 2, 5, 6, and 8 were without cytotoxicity against KB cells in tissue culture at 100 μg/ml.

Experimental Section

General Procedure.§ **6-Methylthio-9-(2′,3′-*O*-isopropylidine-β-D-ribofuranosyl)purine (3).** A mixture of 6-methylthio-9-(β,D-ribofuranosyl)purine (2.0 g, 6.7 mmol), acetone (100 ml), anhydrous copper sulfate (4.0 g), and concentrated sulfuric acid (4 drops) was stirred in a stoppered flask for 4 days. The suspension was filtered and the

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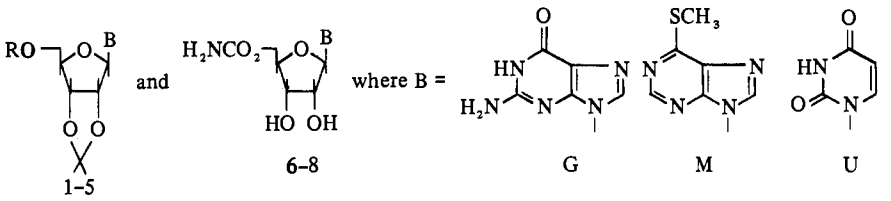
‡Screening was performed under the auspices of DR&D according to the protocols described in ref. 12.

§See Table I for additional details.

Table I. Nucleoside 5'-*O*-Carbamates and Intermediates[a]



No.	B	R	Mp, °C[a] (solvent)	Yield, %	Analyses
1	G	C_6H_5OCO	263–265 (Me_2CO–CH_3OH)[b]	78	C, H, N
2	G	H_2NCO	290–292 (CH_3OH)[b]	76	C, H, N
3	M	H	105–107 (CH_2Cl_2–C_6H_{14})	74	C, H, N, S
4	U	C_6H_5OCO	61–66 (C_6H_{14})[b]	95	
5	U	H_2NCO	178–179 (C_6H_6–CH_3OH)	99	C, H, N
6	G[c]		253–254 (H_2O)	47	C, H, N
7	M[d]		137–138 (C_2H_5OH)	74[e]	C, H, N, S
8	U		149–150 (C_6H_6–CH_3OH)	79	C, H, N

[a]Melting points (uncorrected) were taken on a Fisher-Johns block. [b]Residue after trituration. [c]$[\alpha]^{22}D$ −42.2° (*c* 1.0, DMF). [d]$[\alpha]^{22}D$ −55.1° (*c* 1.0, DMF). [e]Overall yield from 3.

residue was washed with acetone (50 ml). Calcium hydroxide (1.0 g) was added to the filtrate and the suspension was stirred for 1 hr. The solid was filtered out and the solution was evaporated to leave a clear oil. Crystallization from methylene chloride–hexane gave 1.68 g (74%) of white crystals, mp 105–107°.

2',3'-Isopropylidine-5'-*O*-carbophenoxyuridine (4). A suspension of 2',3'-isopropylidineuridine (2.0 g, 7.0 mmol) in pyridine (40 ml) was cooled in ice, and phenyl chloroformate (1.0 ml, 8.3 mmol) was added dropwise with stirring. The solution was stirred in ice for 1 hr and then at room temperature for 1 hr. The solvent was stripped and the residue was treated with methanol (40 ml). The solution was again stripped and the clear residue was triturated with two 40-ml portions of water. The residue was dried by stripping with 1:1 methanol–benzene (80 ml) and then triturated with two 40-ml portions of hot hexane. The residue was dissolved in 1:1 acetone–hexane and stripped to leave a white foam. Trituration with cold hexane gave a white solid, mp 61–66° (2.71 g, 95%), homogeneous by tlc with ethyl acetate on silica gel. This material is satisfactory for the next step.

2',3'-Isopropylidine-5'-*O*-carbamoyluridine (5). A solution of 2',3'-isopropylidine 5'-*O*-carbophenoxyuridine (0.5 g, 1.24 mmol) in methanol (5 ml) and concentrated ammonium hydroxide (15 ml) was stirred at room temperature for 2 hr. Evaporation to dryness left a white foam which was triturated with two 25-ml portions of hot 1:1 benzene–hexane. The oil that remained was dissolved in acetone, filtered, and stripped to leave a white foam. Trituration with hexane gave 0.4 g (99%) of white solid melting at 50–80° and homogeneous by tlc (ethyl acetate).

5'-*O*-Carbamoyluridine (8). A solution of 2',3'-isopropylidine-5'-*O*-carbamoyluridine (2.0 g, 6.1 mmol) in 90% trifluoroacetic acid (40 ml) was left at room temperature for 5 min and then stripped to dryness. The residue was dissolved in ethanol (80 ml) and again stripped to leave a clear gum. Crystallization from 1-propanol gave 1.47 g (70%) of white solid melting at 78–82° and homogeneous by tlc (4:1 ethyl acetate–methanol), $[\alpha]^{22}D$ −0.7° (*c* 1.0, water).

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Hypocholesterolemic Agents. 10.[1] Synthesis of Some Model Azacholanic Acids as Potential Regulators of Steroid Biosynthesis and Metabolism†

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The possible role of cholesterol and other lipids in the etiology of atherosclerosis has focused considerable attention on agents capable of inhibiting cholesterol biosynthesis. One of the physiological sites of regulation in this biosynthesis of cholesterol is thought to be the negative feedback inhibition by cholesterol itself on hydroxymethylglutaryl-CoA reductase, the first irreversible step in this biosynthesis.[2] Previous papers in this series have described the synthesis and potent hypocholesterolemic properties of certain aza- and diazacholesterols which were prepared in an effort to simulate cholesterol in this feedback mechanism. Not only have these compounds been shown to inhibit cholesetrol synthesis in laboratory animals[3] and man,[4] but their ability to interfere with cholesterolgenesis in insects has also been observed.[5]

Since bile acids are end metabolites of cholesterol which also appear to confer a degree of control on cholesterol biosynthesis and are intimately involved in the balance of lipid absorption and excretion in the intestine,[6] it became of interest to examine some model azacholenic acids as potential regulators of steroid biosynthesis and metabolism. This paper represents a continuation of our studies on aza steroids as potential regulators of steroid metabolism and describes the synthesis and biological activities of a number of azacholenic acids.

The most convenient route to C-20 azacholenic and aza-

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