100° yielding 2.1 g (79.5%) of yellow solid, mp 258° dec. *Anal.* ($C_{16}H_{20}N_{10}$) C, H, N.

α,α'-Bis(2,4-diaminoquinazol-6-ylimino)-*p*-xylene and α,α'-Bis-(2,4-diaminoquinazol-6-ylamino)-*p*-xylene (6 and 7). The 2,4,6-triaminoquinazoline was prepared in three steps from anthranilonitrile according to methods described by Davoll and Johnson.[11] A mixture of 4.27 g (0.0244 mol) of this compound and 80 ml of DMF was heated with stirring in a three-necked flask equipped with N_2 purge, addition funnel, thermometer, and condenser. When the temperature reached 90° a solution of 1.48 g (0.011 mol) of terephthaldehyde in 30 ml of DMF was added dropwise (1 hr) and the reaction mixture was then heated at 110–120° for 6 hr. The solid product was collected on a filter, washed with DMF and MeOH, and dried *in vacuo* at *ca.* 160° for 4 hr to give 4.10 g (83%) of orange powder, mp 378–380° dec, suitable for use without further purification. In a separate experiment, a sample of the crude product was recrystallized with low recovery from DMAC yielding a yellow powder, mp 381–383° dec. *Anal.* ($C_{24}H_{20}N_{10}$) C, H, N.

The sample of **6** obtained as above was reduced according to the method of Plante.[10] The crude solid was washed with H_2O and then MeOH and finally recrystallized twice from DMSO–H_2O. After vacuum drying at 100°, there was obtained 2.67 g (61% overall from terephthaldehyde) of 7§ as golden crystals, mp 345–348° dec. *Anal.* ($C_{24}H_{24}N_{10}$) C, H, N.

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§ The synthesis of 7 was reported by Davoll, *et al.*,[12] subsequent to the submission of this paper. They found the compound to be inactive against *Plasmodium berghei* in mice when administered in the diet for 6 consecutive days.

Synthesis of the *S*-Riboside of 5-Mercaptouracil, an "S-Homolog" of Pseudouridine†

Gabor L. Szekeres‡ and Thomas J. Bardos*

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214.
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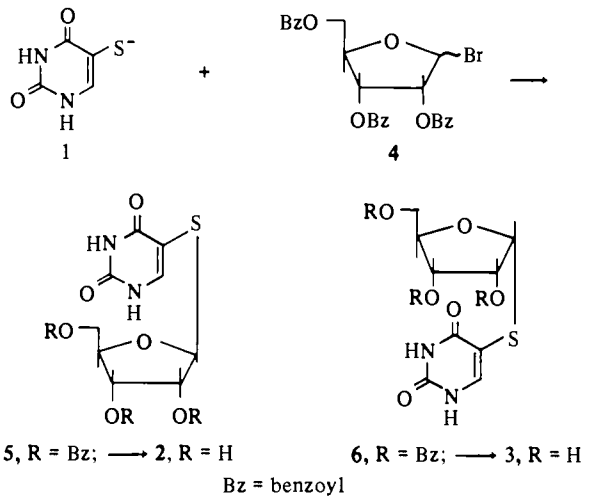
5-Mercaptouracil[1] (**1**) and its nucleosides, 5-mercapto-2'-deoxyuridine[2] (MUdR) and 5-mercaptouridine (MUR),[3] have shown interesting activities in enzymatic,[4] microbiological,[5] and animal tumor[6] systems; MUdR was tested clinically and was found effective in the treatment of skin neoplasms.[7] However, all these 5-mercaptopyrimidine derivatives which, at physiologic pH, are essentially ionized were found to undergo unusually rapid, trace-iron catalyzed autoxidation[8] to the corresponding disulfides; the latter are inert as enzyme substrates[4] and therefore require intracellular reduction[5] before they can be metabolically converted to their active inhibitory (nucleotide) forms. Previous attempts to provide temporary protection to the 5-SH group from oxidation led to the synthesis of a series of *S*-acyl derivatives;[9] these were found to enter into facile transacylation reactions with aliphatic thiols[9] and thus were cleaved in the biological systems to the free mercapto forms in a nonenzymatic manner. In the search for such "protected" derivatives that would require for "deprotection" the action of enzymes present in tumor cells, several *S*-glycosides of **1** have been prepared; a thioglycosidase capable of cleaving certain thioglycosides derived from 6-mercaptopurine had been reported to be present in tumors and other mammalian tissues.[10] The present report deals with the synthesis of *S*-(α- and β-D-ribofuranosyl)-5-mercaptouracils (**2** and **3**). The *S*-(β-D-ribofuranosyl) derivatives of both 8-thioadenine and 6-thiouracil had shown moderate inhibitory activities against L1210 and Ehrlich ascites cells in culture.[11] In addition, **2** is of special interest as a structural analog ("S-homolog") of pseudouridine.

Reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**) with **1** in DMF yielded a mixture of the two anomeric blocked *S*-ribosides, **5** and **6**. The anomeric mixture was purified by column chromatography on silicic acid, and the two anomers were then separated by fractional crystallization from benzene. Debenzoylation of **5** and **6** yielded the free *S*-ribofuranosides **2** and **3**, respectively.



The anomeric configurations were assigned on the basis of the pmr spectra of **2** and **3**; in making the assignments, the relative positions of the signals attributed to the anomeric protons (signal at higher field corresponding to the β anomer) were considered a more reliable criterion (in the case of ribofuranosides)[12] than the $J_{1'2'}$ coupling constant. The fact that both the α and β anomers were obtained in the above "coupling reaction" of **4** with **1** is in contrast to the finding of Shuman, *et al.*,[11] who isolated only the blocked β-*S*-glycosides from the reactions of the corresponding chloro sugar with the sodium salts of 8-mercaptoadenine and of 6-thiouracil, but it is consistent with our previously proposed interpretation[2,3] of the "coupling reactions" of such halogenoses as **4**, *i.e.*, that, in

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the absence of a heavy metal salt, they proceed preferentially *via* an SN2 mechanism.

Both **2** and **3** were found to be inactive in the *Lactobacillus leichmannii* assay system[5a] in which **1** shows significant inhibition under the same assay conditions. Preliminary testing of **2** and **3** against the L1210 and Ehrlich ascites cell lines in cultures[13] showed no significant inhibitory activity. It appears that the thioglycoside bonds in **2** and **3** are not cleaved by the cells and that these derivatives as such (as the structurally analogous pseudouridine itself) are inactive in these assay systems. However, **2** may be of future interest in studies relating to pseudouridine.

Experimental Section

Melting points were taken in open capillary tubes on a Mel-temp apparatus and are uncorrected. Nmr spectra were recorded on a Varian Model A-60 spectrophotometer in D_2O with *t*-BuOH as internal standard. Optical rotations were measured in a 1-dm tube using a Perkin-Elmer Model 141 automatic polarimeter at 589 mμ. Evaporations were carried out under reduced pressure on a rotary evaporator at 40° bath temperature. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Anomeric *S*-(2',3',5'-Tri-*O*-benzoyl-D-ribofuranosyl)-5-mercaptouracils (5 and 6). To a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 10.08 g (20 mmol) of 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose according to Stevens, *et al.*[12b]) in anhydrous DMF (80 ml) was added 5-mercaptouracil[1] (3.16 g, 22 mmol) and Et_3N (3.1 ml, 22 mmol). After the solution was stirred under N_2 atmosphere overnight, H_2O (5 ml) was added, and the solvent was evapoated. The residue was dissolved in $CHCl_3$ and filtered, and the $CHCl_3$ solution was concentrated and applied to a column packed with 300 g of silicic acid in $CHCl_3$. After the elution of some impurities (decomposition products of **4**) with $CHCl_3$, **5** and **6** were eluted, together, with $CHCl_3$–EtOAc (1:3). After pooling and evaporation of the fractions which appeared homogenous by tlc, a mixture of the two anomers was obtained as a solid foam (5.45 g, 46.4%). Heating of this residue in C_6H_6 resulted in rapid dissolution followed by immediate precipitation of **5** as a white powder, 3.74 g, 31.8%, mp 193–196°. Recrystallization from C_6H_6 furnished a sample for analysis, mp 198–199°, $[\alpha]D$ −101.1° (*c* 2.3, $CHCl_3$). *Anal.* ($C_{30}H_{24}N_2O_9S$) C, H, N, S.

The C_6H_6 mother liquor was concentrated to dryness to give **6** as a solid foam (1.05 g, 8.95%). This was purified for analysis by repeated dissolution in C_6H_6 and precipitation with hexane, mp 95–115°, $[\alpha]D$ 111.3° (*c* 0.68, $CHCl_3$). *Anal.* ($C_{30}H_{24}N_2O_9S$) C, H, N, S.

***S*-(β-D-Ribofuranosyl)-5-mercaptouracil (2).** To a suspension of **5** (1.176 g, 2 mmol) in anhydrous MeOH (50 ml) was added $NaOCH_3$, freshly prepared from Na metal (0.092 g, 4 mg-atoms) in MeOH (10 ml), and the resulting solution was stirred for 5 hr. Dowex 50 W × 8 resin, H^+ form (10 ml wet volume in MeOH), was then added. After 10 min the resin was removed by filtration and MeOH concentrated to 15 ml. Crystals deposited on standing at 5°, were collected by filtration, and washed with Et_2O (0.459 g, 83%). After recrystallization from MeOH, the following data were obtained: mp 222–224°; $[\alpha]D$ −142.9° (*c* 0.8, H_2O); nmr (D_2O) anomeric proton δ 5.12 ppm (d, *J* = 3.8 Hz). *Anal.* ($C_9H_{12}N_2O_6S$) C, H, N, S.

***S*-(α-D-Ribofuranosyl)-5-mercaptouracil (3).** **6** (0.589 g, 1 mmol) was debenzoylated as described above for the deblocking of **4** to give **3** (0.170 g, 61.5%). After recrystallization from MeOH, the following data were obtained: mp 156–160°; $[\alpha]D$ 291.0° (*c* 0.5, H_2O); nmr (D_2O) anomeric proton δ 5.85 ppm (d, *J* = 5.0 Hz). *Anal.* ($C_9H_{12}N_2O_6S$) C, H, N, S.

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1-Glycosyl Derivatives of 5-Aminoimidazole-4-carboxamide†,‡

John A. Montgomery* and H. Jeanette Thomas

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. *Received May 24, 1972*

The 5'-phosphate of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide is a key intermediate in the *de novo* biosynthesis of purine ribonucleotides. Formylation of this compound followed by ring closure gives rise to inosinic acid.[1] Various compounds known to interfere with *de novo* purine biosynthesis have shown anticancer activity. It was, therefore, of interest to investigate the synthesis and evaluation of analogs of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**5b**), since nucleotides themselves cannot penetrate cell membranes. A kinase capable of phosphorylating **5b** has been found in yeast[2] and more recently the biologically active form of pyrazomycin, a closely related nucleoside, has been identified as its 5'-phosphate formed *in vivo*.[3]

A logical approach to the synthesis of imidazole nucleosides pursued by Shaw[4-6] involves the substitution at N-1 of inosine of a removable group that causes base lability of the pyrimidine ring. Shaw used the benzyl,[4] *p*-toluenesulfonyl,[5] and the methoxymethyl[6] groups, but none of these groups appeared to us to be entirely satisfactory. We decided to employ the benzyloxy group, which proved very effective in the synthesis of 5-aminoimidazole-4-carboxamidines.[7] 9-Cyclopentyladenine 1-oxide[7] (**1a**) was deaminated by treatment with sodium nitrite in dilute acetic acid. The resultant 9-cyclopentyl-1-hydroxyhypoxanthine (**2a**) was resistant to aqueous base treatment due, no doubt, to anion formation at the 1-hydroxy position,[8] which prevents attack of the hydroxide ion at C-2 of the purine ring. Benzylation of **2a** with benzyl bromide with DMA gave 1-benzyloxy-9-cyclopentylhypoxanthine (**3a**) as shown by a strong carbonyl doublet centered at 1700 cm^{-1} in its infrared

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