

HCl giving a white gelatinous solid: tlc (DMF-H₂O, 19:1) *R_f* 0.76. 2-Amino-4-hydroxy-6-methylpteridine (8) was reported to have *R_f* 0.65 under the same conditions.⁹

2-Amino-4-hydroxy-7-(1-adamantyl)pteridine (7). 2,4-Diamino-7-(1-adamantyl)pteridine (2) (25 mg) was refluxed with 20 ml of 0.1 *N* NaOH for 96 hr under N₂. A gelatinous solid was obtained on neutralization with 1 *M* HCl: tlc (DMF-H₂O, 19:1) *R_f* 0.95. 2-Amino-4-hydroxy-7-methylpteridine (9) was reported to have *R_f* 0.88 under the same conditions.⁹

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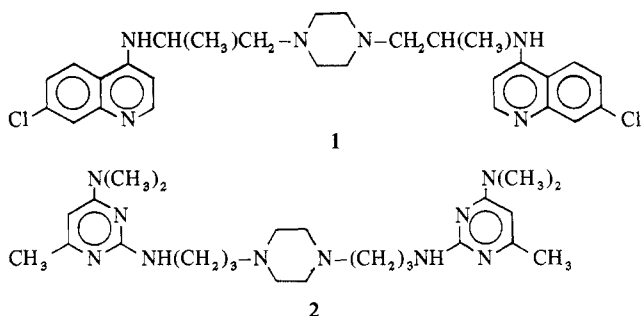
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Synthesis of Some Bis(2,4-diaminopyrimidines) and Bis(2,4-diaminoquinazolines) as Potential Antimalarial Agents†

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There are numerous examples of symmetric molecules throughout medicinal chemistry. In the chemotherapy area suramin,¹ dapsone,² pentamidine,³ and $\alpha,\alpha,\alpha,\alpha',\alpha',\alpha'$ -hexachloro-*p*-xylene⁴ are important examples. Recently, several high molecular weight compounds bearing identical terminal heterocyclic rings such as 1 and 2 have been shown to display significant antimalarial activity.^{5,6} In addition, certain members of a series of bis(4,6-diamino-1,2-dihydro-*s*-tri-



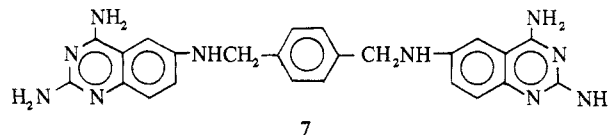
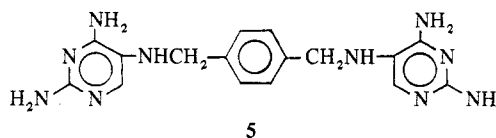
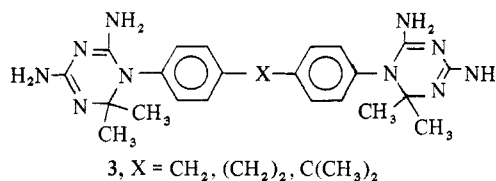
azines), 3, were shown to be moderately potent inhibitors of *Streptococcus faecalis* and dihydrofolate reductase (pigeon liver) *in vitro*.⁷ Therefore, α,α' -bis(2,4-diaminopyrimid-5-ylamino)-*p*-xylene (5) and α,α' -bis(2,4-diaminoquinazol-6-ylamino)-*p*-xylene (7) were prepared and evaluated for antimalarial activity and as inhibitors of mammalian dihydrofolate reductase. Neither of these nor their corresponding dianils, 4 and 6, from which they were pre-

Table I. Enzyme Inhibition Study of Mammalian Dihydrofolate Reductase

Compd	<i>I</i> ₅₀ , μ M ^a
4	>10 ^b
5	2.0
6	1.4
7	0.45
Pyrimethamine	0.07 ^c

^a Assayed spectrophotometrically (340 m μ) with 9 μ M dihydrofolate, 30 μ M NADPH, and 0.15 *M* KCl in 0.05 *M* Tris buffer (pH 7.4). ^b Compound did not possess sufficient solubility for determination. ^c R. Ferone, J. J. Burchall, and G. H. Hitchings [*Mol. Pharmacol.*, **5**, 49 (1969)] reported 0.7 μ M for pyrimethamine using 50 μ M dihydrofolate.

pared, showed activity against *Plasmodium berghei* in mice.^{8,†} Compound 7 was the best inhibitor of rat liver dihydrofolate reductase, cf. Table I, being three to four times more potent than its rigid dianil, 6, or its pyrimidine counterpart, 5, but was still considerably less potent than pyrimethamine.



Experimental Section

Melting points were taken with a Mel-Temp apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, the results were within $\pm 0.4\%$ of the theoretical values.

Enzyme Assay. Frozen rat liver was processed according to the method of Baker⁹ to yield a crude solution of dihydrofolate reductase which upon appropriate dilution was suitable for the inhibition assay. Inhibitors were dissolved in DMSO (1.0 mM or 0.1 mM concentration) and diluted to the desired concentration with 1 mM HCl before addition to the assay buffer. The assay procedure was essentially the same as that described by Baker.⁹ Any change in absorbance due to NADPH oxidase activity was subtracted by use of a reference cell containing only enzyme and NADPH in buffer, which was prepared just prior to each run.

α,α' -Bis(2,4-diaminopyrimid-5-ylamino)-*p*-xylene (4). To a slurry of 10.2 g (0.044 mol) of 2,4,5-triaminopyrimidine sulfate hemihydrate in 75 ml of methoxyethanol (N₂ purge) was added dropwise with stirring 2.02 g (0.088 mol) of Na in 35 ml of methoxyethanol. The resulting dark solution was treated with MgSO₄, filtered, and then placed in a 200-ml flask containing 2.68 g (0.02 mol) of terephthalaldehyde and refluxed for 3.5 hr. The resulting solid was separated by filtration, washed with EtOH, and dried. Recrystallization from DMAC, followed by washing with EtOH, Et₂O, and vacuum drying at 100° for 2 hr, produced 2.0 g (29%) of orange powder, mp 324–326° dec. *Anal.* (C₁₆H₁₆N₁₀) C, H, N.

α,α' -Bis(2,4-diaminopyrimid-5-ylamino)-*p*-xylene (5). This reduction was conducted according to the method of Plante¹⁰ using dimethylamineborane. The crude product was recrystallized from DMAC, washed with EtOH (hot) and Et₂O, and vacuum dried at

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‡ Testing of all compounds was carried out by Dr. L. Rane of the University of Miami.

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 anthranilnitrile 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†

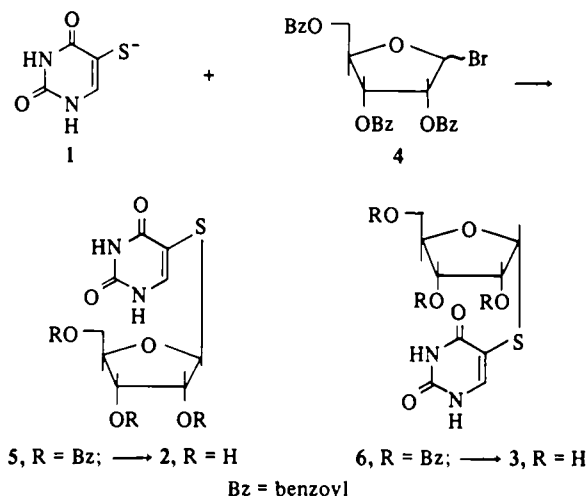
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5-Mercaptouracil¹ (1) and its nucleosides, 5-mercapto-2'-deoxyuridine² (MUdR) and 5-mercaptouridine (MUR),³ have shown interesting activities in enzymatic,⁴ micro-

biological,⁵ and animal tumor⁶ 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 autoxidation⁸ to the corresponding disulfides; the latter are inert as enzyme substrates⁴ and therefore require intracellular reduction⁵ 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 thiols⁹ 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-mercaptouracil 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-mercaptouracil 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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