HCl giving a white gelatinous solid: tlc (DMF–H_2O, 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 N_2. A gelatinous solid was obtained on neutralization with 1 *M* HCl: tlc (DMF–H_2O, 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]

References

(1) J. P. Jonak, S. F. Zakrzewski, and L. H. Mead, *J. Med. Chem.*, 15, 662 (1972).
(2) A. Albert, *Quart. Rev., Chem. Soc.*, 6, 197 (1952).
(3) I. J. Pachter, *J. Org. Chem.*, **28**, 1191 (1963).
(4) J. Bernstein, U. S. Patent 3,465,041 (1969).
(5) (a) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **71**, 1753 (1949); (b) J. H. Mowat, J. H. Boothe, B. L. Hutchings, E. L. R. Stokstad, C. W. Waller, R. B. Angier, J. Semb, D. B. Cosulich, and Y. SubbaRow, *ibid.*, **70**, 14 (1948).
(6) J. P. Jonak, S. F. Zakrzewski, and L. H. Mead, *J. Med. Chem.*, 14, 408 (1971).
(7) A. Bloch and C. A. Nichol, *Antimicrob. Ag. Chemother.*, 530 (1964).
(8) A. Bloch and C. Coutsogeorgopoulos, *Biochemistry*, 10, 4394 (1971).
(9) B. Nicolaus, *J. Chromatogr.*, 4, 384 (1960).

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

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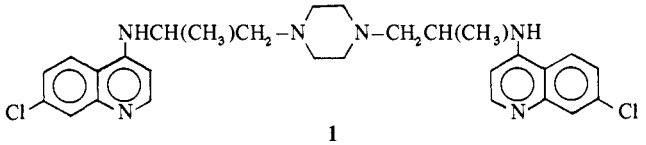
There are numerous examples of symmetric molecules throughout medicinal chemistry. In the chemotherapy area suramin,[1] dapsone,[2] pentamidine,[3] and α,α,α,α′,α′,α′-hexachloro-*p*-xylene[4] are important examples. Recently, several high molecular weight compounds bearing identical terminal heterocyclic 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-



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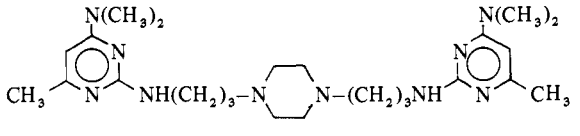

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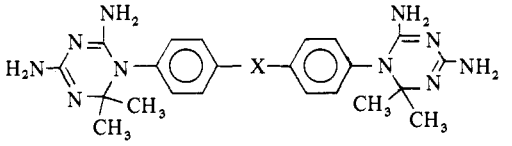
azines), **3**, were shown to be moderately potent inhibitors of *Streptococcus faecalis* and dihydrofolate reductase (pigeon liver) *in vitro*.[7] Therefore, α,α′-bis(2,4-diaminopyrimid-5-ylamino)-*p*-xylene **(5)** and α,α′-bis(2,4-diaminoquinazol-6-ylamino)-*p*-xylene **(7)** were prepared and evaluated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

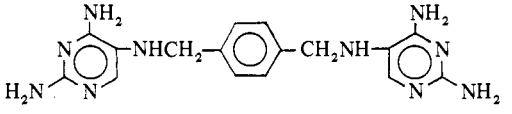
Table I. Enzyme Inhibition Study of Mammalian Dihydrofolate Reductase

Compd	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 mμ) 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.



3, X = CH_2, $(CH_2)_2$, $C(CH_3)_2$



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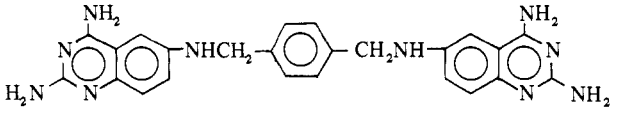

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Experimental Section

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 ±0.4% of the theoretical values.

Enzyme Assay. Frozen rat liver was processed according to the method of Baker[9] 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 m*M* or 0.1 m*M* concentration) and diluted to the desired concentration with 1 m*M* 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-ylimino)-*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 (N_2 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 $MgSO_4$, filtered, and then placed in a 200-ml flask containing 2.68 g (0.02 mol) of terephthaldehyde 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, Et_2O, and vacuum drying at 100° for 2 hr, produced 2.0 g (29%) of orange powder, mp 324–326° dec. *Anal.* ($C_{16}H_{16}N_{10}$) C, H, N.

α,α′-Bis(2,4-diaminopyrimid-5-ylamino)-*p*-xylene (5). This reduction was conducted according to the method of Plante[10] using dimethylamineborane. The crude product was recrystallized from DMAC, washed with EtOH (hot) and Et_2O, 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 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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References

(1) M. Mayer and H. Zeiss, *Arch. Schiffs. Tropen.-Hyg.*, **24**, 257 (1920).
(2) N. Rist, *C. R. Soc. Biol.*, **130**, 972, 976 (1939).
(3) E. M. Lourie and W. Yorke, *Ann. Trop. Med. Parasitol.*, **33**, 289 (1939).
(4) E. F. Elslager, M. P. Hutt, and L. M. Werbel, *J. Med. Chem.*, **13**, 542 (1970).
(5) T. R. Castles, E. Loth, C. R. Crawford, and C. C. Lee, *J. Pharmacol. Exp. Ther.*, **172**, 44 (1970).
(6) E. Schweizer, U. S. Patent 3,503,977 (1970).
(7) D. B. Capps, O. D. Bird, E. F. Elslager, Z. B. Gavrilis, J. A. Roush, P. E. Thompson, and J. W. Vaitkus, *J. Heterocycl. Chem.*, **5**, 355 (1968).
(8) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(9) B. R. Baker and G. J. Lourens, *ibid.*, **10**, 1113 (1967).
(10) L. T. Plante, *J. Org. Chem.*, **36**, 860 (1971).
(11) J. Davoll and A. M. Johnson, *J. Chem. Soc. C*, 997 (1970).
(12) J. Davoll, A. M. Johnson, H. J. Davies, O. D. Bird, J. Clarke, and E. F. Elslager, *J. Med. Chem.*, **15**, 812 (1972).

§ 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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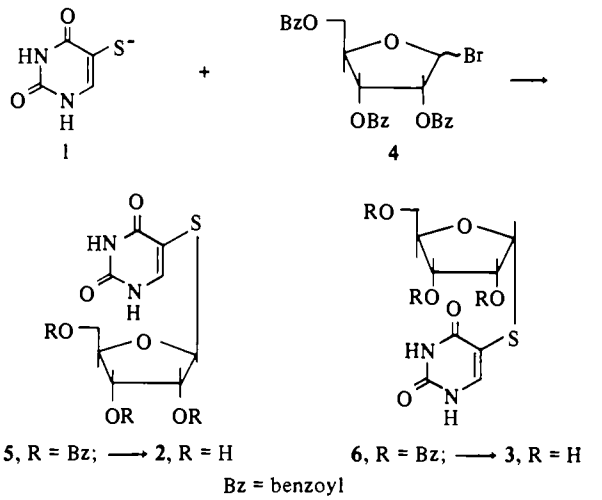
5-Mercaptouracil[1] (**1**) and its nucleosides, 5-mercapto-2'-deoxyuridine[2] (MUdR) and 5-mercaptouridine (MUR),[3] have shown interesting activities in enzymatic,[4] microbiological,[5] and animal tumor[6] systems; MUdR was tested clinically and was found effective in the treatment of skin neoplasms.[7] 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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