anhydrous Et_2O (20 ml) and absolute C_2H_5OH. Anhydrous HCl was passed through the soln. On cooling, the hydrochloride was isolated.

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Synthesis and Biological Activity of 2,4-Diamino-6- and -7-(1-adamantyl)pteridines[†]

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As part of an effort to synthesize new folate antagonists[1] of potential anticancer activity, we would like to report the preparation and some biological properties of 2,4-diamino-6-(1-adamantyl)pteridine (**1**) and its isomer, 2,4-diamino-7-(1-adamantyl)pteridine (**2**). Compound **1** was obtained by condensation of 1-adamantylglyoxal hydrazone[§] (**3**) with 2,4,5,6-tetraaminopyrimidine hydrochloride[3] in aqueous methanol. Isomeric pteridine **2** was prepared by condensation of 1-adamantylglyoxal[4] with 2,4,5,6-tetraaminopyrimidine[3] in methanol.[#]

The structural assignments of the two isomers were established by comparison of their uv maxima with the literature values recorded for 2,4-diamino-6- and -7-methylpteridines (Table I), **4** and **5**, respectively. Hydrolysis of the diaminoadamantylpteridines (**1** and **2**) gave the respective 2-amino-4-hydroxypteridines (**6** and **7**) which had uv spectra (Table I) and tlc characteristics (Experimental Section) similar to the literature values for 2-amino-4-hydroxy-6- and -7-methylpteridines (**8** and **9**, respectively).

Compound **1** was found to inhibit the growth of mouse mammary adenocarcinoma (TA3) cells *in vitro* culture[6] with an ID_{50} of $1.4 \times 10^{-7}M$. This compound also inhibited the growth of *Streptococcus faecium*[7] with an ID_{50} of 1.44×10^{-8} M but was an ineffective growth inhibitor of *Escherichia coli*[8] at a concentration of $10^{-5}M$.

Compound **2** demonstrated growth inhibition of the TA3 cells with ID_{50} $4.8 \times 10^{-6}M$. Compound **2** also inhibited the growth of *Strep. faecium*[7] with ID_{50} $1.96 \times 10^{-6}M$ but was an ineffective growth inhibitor of *E. coli*[8] at a concentration of $10^{-5}M$.

It is possible that the activity of the 7 isomer (**2**) is affected by very minor amounts of the 6 isomer present as an impurity. The biological data seem to negate this objection because the ratios of the ID_{50}'s (2:1) for the TA3 cells and *Strep. faecium* are 35 and 136, respectively. One would expect these ratios to be nearly the same if the activity of **2**

§Use of the hydrazone has been shown to produce the 6 isomer in analogous systems (see ref 2).

#Use of these conditions has been shown to lead to the 7 isomer in analogous systems (see ref 2).

Table I. Ultraviolet Data[a]

No.	R	R^1	R^2	λ_{max}, mμ pH 1	λ_{max}, mμ pH 13
1	NH_2	$C_{10}H_{15}$[b]	H	338	369
2	NH_2	H	$C_{10}H_{15}$[b]	331	360
4	NH_2	CH_3	H	337[c]	369[c]
5	NH_2	H	CH_3	332[c]	361[c]
6	OH	$C_{10}H_{15}$[b]	H	324	364
7	OH	H	$C_{10}H_{15}$[b]	316	357
8	OH	CH	H	326[d]	367[d]
9	OH	H	CH_3	319[d]	359[d]

[a]Other maxima present in each spectrum are not presented here for the sake of clarity. Shifts of the maxima not presented are in the same direction as those reported in this Table. [b]1-Adamantyl. [c]Seeger, *et al.*[5a] [d]Mowat, *et al.*[5b]

were an artifact caused by isomeric contamination of the analytical sample.

Work is continuing in our laboratories to determine if other adamantylpteridines will exhibit biological activity.

Experimental Section

Analytical data were obtained by G. I. Robertson, Jr., Florham Park, N. J.; where analyses are indicated by the symbols of the elements, analytical results were within ±0.3% of the theoretical values. Ultraviolet spectra were run on a Perkin-Elmer 202. Tlc plates were Brinkman silica gel F-254 on aluminum. Melting points were determined on a Fisher-Johns apparatus.

1-Adamantylglyoxal Hydrazone (3). 1-Adamantylglyoxal[4] (1.68 g, 8.75 mmoles) was dissolved in the min amt of abs Et_2O. A few drops of hydrazine were added to this soln. A ppt began to form almost immediately and was collected after 0.5 hr. The crude material (1.2 g) was recrystallized from Et_2O to give 300 mg: mp 132–135°; single spot in tlc ($CHCl_3$-THF, 1:1) R_f 0.33. *Anal.* ($C_{12}H_{18}N_2O$) C, H, N.

2,4-Diamino-6-(1-adamantyl)pteridine (1). 1-Adamantylglyoxal hydrazone (**3**) (300 mg, 1.46 mmoles) in MeOH (40 ml) was added to a soln of 2,4,5,6-tetraaminopyrimidine hydrochloride[3] in a hot soln of 35 ml of MeOH and 5 ml of H_2O. This reaction mixt was stirred under N_2 for 18 hr; during this period of time, the vol decreased from 75 to 40 ml. The reaction mixt was then evapd to dryness. The resulting residue was extracted twice with hot EtOH–THF (1:4). The insol solid was unreacted pyrimidine (140 mg) (tlc). The filtrates were evapd to dryness and triturated with Et_2O to give 90 mg of gray-white solid which was dissolved in hot EtOH and filtered. Enough H_2O was added to the soln to make it opaque, and the soln was allowed to cool to room temperature. The solid was collected by filtration, washed with Et_2O, and dried at 138° *in vacuo* over P_2O_5 for 4 hr to give **1**: 50 mg yield; mp 326–328° dec; tlc (ϵ 9.8 × 10³) (THF–$CHCl_3$, 1:1) single spot, R_f 0.18; λ_{max} (pH 1) 243 (ϵ 1.76 × 10⁴), 279 (3.8 × 10³), 338 mμ; λ_{max} (pH 13) 257 (ϵ 1.65 × 10⁴), 369 mμ (5.76 × 10³). *Anal.* ($C_{16}H_{20}N_6$·0.75HCl) C, H, C; N: calcd, 26.00; found, 25.42.

2,4-Diamino-8-(1-adamantyl)pteridine (2). A soln of 1-adamantylglyoxal[4] (905 mg, 4.0 mmoles) in hot MeOH (100 ml) was added to a soln of 2,4,5,6-tetraaminopyrimidine hydrochloride[3] in MeOH (100 ml, hot). The reaction mixt turned yellow immediately and was refluxed for 2.5 hr. The vol was reduced to 30 ml, the reaction mixt cooled, and 360 mg of product collected on filtration. Recrystallization from abs EtOH gave 460 mg: mp (darkens from 265°) 307–309° dec, after drying at 138° over P_2O_5 *in vacuo* for 2 hr; tlc (THF–$CHCl_3$, 1:1) R_f 0.36 (single spot); λ_{max} (pH 1) 239 (ϵ 1.92 × 10⁴), 277 (7.84 × 10³), 331 mμ (1.63 × 10⁴); λ_{max} (pH 13) 252 (ϵ 1.33 × 10⁴), 360 mμ (6.47 × 10³). *Anal.* ($C_{16}H_{20}N_6$·C_2H_5OH·HCl) C, H, N, Cl.

Hydrolysis of 2,4-Diamino-6- and -7-(1-adamantyl)pteridines. 2-Amino-4-hydroxy-6-(1-adamantyl)pteridine (6). 2,4-Diamino-6-(1-adamantyl)pteridine (**1**) (3 mg) was refluxed under N_2 with 3 ml of 0.1 N NaOH for 2 hr when soln occurred. After 2 hr more, the reaction mixt was cooled and the basic soln neutralized with 1 N

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]

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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*-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-


1

2
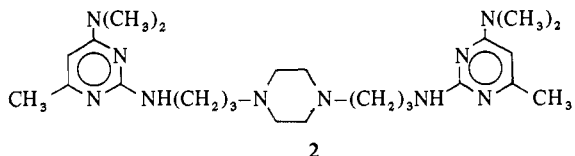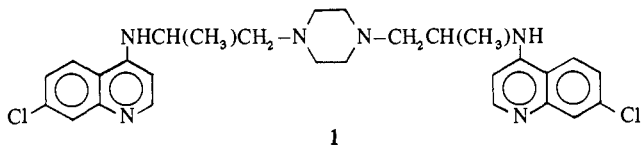
azines), 3, were shown to be moderately potent inhibitors of *Streptococcus faecalis* and dihydrofolate reductase (pigeon liver) *in vitro.*[7] Therefore, α,α'-bis(2,4-diaminopyrimid-5-ylamino)-*p*-xylene (5) and α,α'-bis(2,4-diaminoquinazol-6-ylamino)-*p*-xylene (7) were prepared and evaluated for antimalarial 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	$I_{50}, \mu M^a$
4	$>10^b$
5	2.0
6	1.4
7	0.45
Pyrimethamine	0.07^c

^{a}Assayed spectrophotometrically (340 mμ) with 9 μM dihydrofolate, 30 μM 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 μM for pyrimethamine using 50 μM 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.

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

5

7
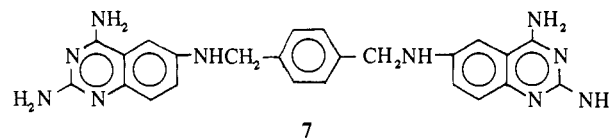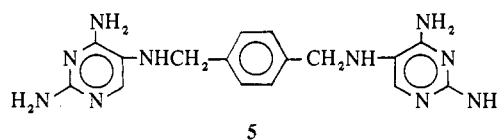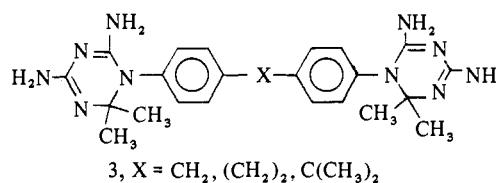
Experimental Section

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