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Pteridines. 2. New 6,7-Disubstituted Pteridines as Potential Antimalarial and Antitumor Agents†,[1]

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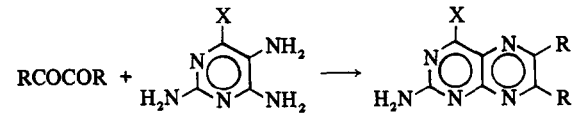
A number of new 6,7-disubstituted 2,4-diaminopteridines (**1**) and 2-amino-4-hydroxypteridines (**2**) were synthesized for biological evaluation *via* the Isay reaction of symmetrical α-diketones with 2,4,5,6-tetraaminopyrimidine and 2,4,5-triamino-6-hydroxypyrimidine, respectively. For the synthesis of 6,7-bis(arylmethyl)pteridines, it was found that 1,4-diaryl-2,3-butanediones can be replaced by 2,5-diaryl-2,3-dihydrothiophen-4-ol-3-one 1,1-dioxides (**3**), which are known to be converted into α-diketones on Zn metal reduction to 2,5-diaryl-2,3,4,5-tetrahydrothiophen-4-ol-3-one 1,1-dioxides (**4**) followed by SO_2 elimination. A useful preparative method was developed whereby conversion of **3** into **1** (R = $ArCH_2$) or **2** (R = $ArCH_2$) was effected in a single continuous operation without isolation of either **4** or the α-diketone. Condensation of **3** with 2,4,5-triamino-6-hydroxypyrimidine led to 2-amino-6,8-diaryl-6,8-dihydrothieno[3,4-*g*]pteridine 7,7-dioxides (**5**), the first examples of a new heterocyclic ring system. 2-Amino-6-benzyl-4-hydroxypteridine (**6**) and 2-amino-7-benzyl-4-hydroxypteridine (**7**) were prepared from 1,1-dimethoxy-3-phenyl-2-propanone (**8**), and their identity was established on the basis of nmr spectra in 4:1 CF_3CO_2H–FSO_3H solution. Reduction of **6** with Zn in NaOH yielded the 7,8-dihydro derivative **9**, whereas catalytic hydrogenation in CF_3CO_2H led to the 5,6,7,8-tetrahydro compound **10**. The 2,4-diaminopteridines were potent inhibitors of the folate-requiring organism *Streptococcus faecium* (ATCC No. 8043), but no significant antimalarial or antitumor activity was observed with any of the compounds tested.

A number of symmetrically 6,7-disubstituted 2,4-diaminopteridines[2-4] have been reported to possess antibacterial[5-11] and antimalarial[11-17] properties, although significant antitumor activity has not been found.[18] Recent enzyme studies with purified dihydrofolate reductase of mammalian and nonmammalian origin[19,20] tend to support earlier indications that large hydrophobic substituents at positions 6 and 7 exert a favorable effect on the activity as well as the species selectivity of these compounds.[21] In this paper, as part of a broader survey of new folate antagonists as candidate antimalarial and experimental antitumor agents,[22] we wish to report the synthesis of some 2,4-diamino-6,7-bis(aralkyl)-pteridines (**1**, Table I) from α-diketones and 2,4,5,6-tetraaminopyrimidine *via* the Isay reaction.[23,24] Also prepared from the same α-diketones and 2,4,5-triamino-6-hydroxypyrimidine were the corresponding 2-amino-6,7-bis(aralkyl)-4-hydroxypteridines (**2**, Table I). Application of the Isay reaction for the synthesis of a variety of symmetrical 6,7-disubstituted pteridines, including some 2,4-diamino and 2-amino-4-hydroxy derivatives, was reported by us some time ago.[25] 2-Amino-4-hydroxy-6,7-bis(aralkyl)pteridines were of particular interest because of the possibility that, on reduction to the tetrahydro form *in vivo*, they might act as inhibitors of thymidylate synthetase.[26-28] Of added interest were reports concerning the possible role of reduced 2-amino-4-hydroxypteridines in enzymatic aromatic hydroxylations[29-33] and in the biosynthesis of fatty acids.[34]



1, X = NH_2
2, X = OH

Chemistry. 6,7-Disubstituted 2,4-diaminopteridines synthesized by previous workers have contained, in nearly every instance, straight or branched chain alkyl groups,[2,3] aromatic rings,[2] or a fused cycloalkane moiety.[4,35,36] The 6,7-dibenzyl derivative has also been reported,[3] but no analogs with substituted benzyl groups were known when this work was begun. In the hope of enlarging our understanding of the structure–activity relationships among 2,4-diaminopteridine antifolates, we therefore chose to focus our synthetic efforts upon variants of this type, as well as some in which the phenyl ring is separated from the pteridine moiety by more than one methylene unit.

α-Diketones required for the Isay reaction are usually accessible in good yields *via* the acyloin condensation. However, this approach is inappropriate for the synthesis of 1,4-diaryl-2,3-butanediones, especially when aromatic halogen

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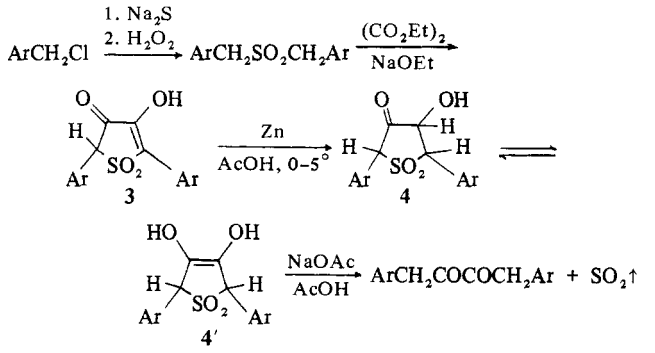
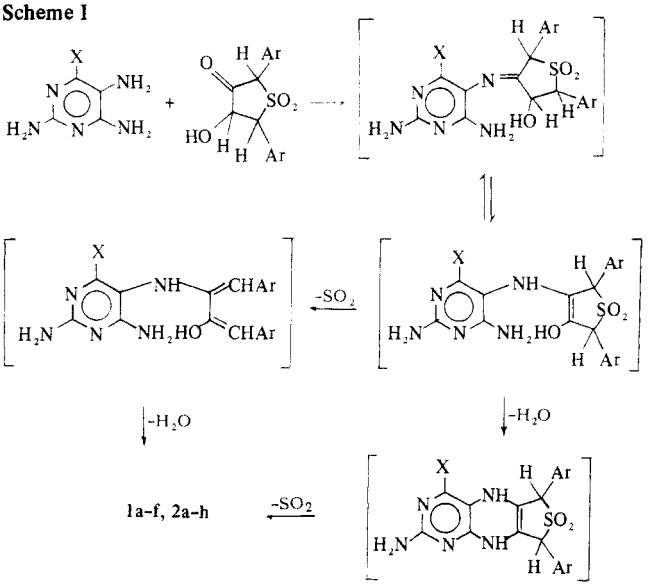
substituents are desired. A useful alternative route has been developed in our laboratory which permits 1,4-diaryl-2,3-butanediones to be obtained rapidly and in high yield.[37] In this procedure a substituted benzyl chloride is converted *via* three straightforward steps into a cyclic sulfone **3**[38] which on treatment with Zn in AcOH-EtOH-THF at 0-5° undergoes reduction to the isolable intermediate **4**. When **4** is heated in the presence of a weak base, a ring cleavage occurs giving the desired α-diketone and SO_2, presumably *via* a concerted process involving enediol tautomer **4'**.[37]



As indicated by the examples given in the Experimental Section and in Table I, we have found that 2,4-diamino-6,7-bis(aralkyl)pteridines may be prepared from 2,4,5,6-tetraaminopyrimidine according to three different procedures employing α-diketones (procedure A), tetrahydrothiophen-4-ol-3-one 1,1-dioxides (**4**) (procedure B), or dihydrothiophen-4-ol-3-one 1,1-dioxides (**3**) (procedure C). Similar use of 2,4,5-triamino-6-hydroxypyrimidine leads to the formation of 2-amino-4-hydroxypteridines. Yields generally tend to fall in the 40-70% range in both series. For preparative purposes, it is most convenient to proceed directly from the cyclic sulfone **3** to the pteridine without isolating either **4** or the α-diketone (Table I, procedure C). This has a practical advantage in that the stability of the cyclic sulfones **3** makes them more suitable for storage than the α-diketones **5**, some of which tend to deteriorate on standing. Although some α-diketone is undoubtedly formed in the one-step method, we believe that formation of a pteridine from cyclic sulfone **4** takes place in part *via* a mechanism involving Schiff base formation prior to SO_2 elimination and ring closure (Scheme I).

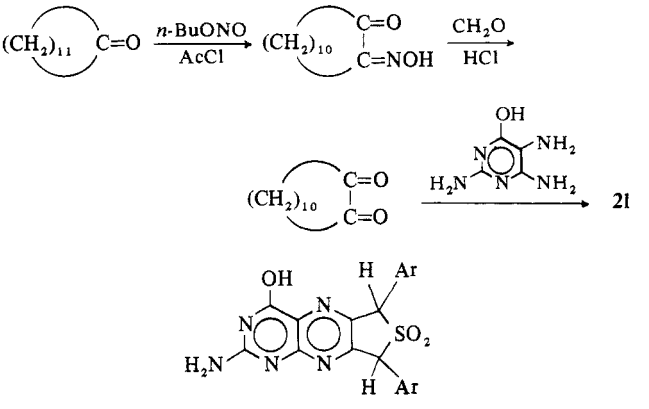
The known 6,7-bis(cyclohexylmethyl) analog **1g**[3] as well as the heretofore undescribed 6,7-bis(2-phenylethyl) and 6,7-bis(3-phenylpropyl) analogs **1h** and **1i** was obtained from 2,4,5,6-tetraaminopyrimidine and the corresponding α-diketones which were accessible without difficulty *via* the normal acyloin route. Likewise, the 2-amino-4-hydroxypteridines **2i-k** were synthesized from 2,4,5-triamino-6-hydroxypyrimidine. In contrast to previous workers who reported that 1,6-diphenyl-3,4-hexanedione is formed directly in the acyloin reaction,[39] we succeeded in obtaining the α-diketone only after separate oxidation of the crude

Scheme I



acyloin with $Cu(OAc)_2$. Compounds **1h**, **1i**, **2j**, and **2k** are of interest as analogs of the recently described 6-monosubstituted congeners.[40,41]

The 6,7-decamethylene analog **2l** was synthesized straightforwardly from cyclododecanone in three steps. Reaction of the ketone with *n*-BuONO in the presence of acetyl chloride[42] led to the α-oximino derivative. Further reaction with formalin and HCl[43] afforded 1,2-cyclododecanedione and condensation of the latter with 2,4,5-triamino-6-hydroxypyrimidine yielded the pteridine. For preparative convenience the entire reaction sequence can be carried out without purifying the α-oximino derivative or the α-diketone.



Condensation of the cyclic sulfones **3** with 2,4,5-triamino-6-hydroxypyrimidine without prior SO_2 extrusion yielded the thieno[3,4-*g*]pteridines **5** (Table I) which were of interest because of recent reports describing the analogous preparation of thieno[3,4-*g*]quinoxalines from *o*-phenyl-

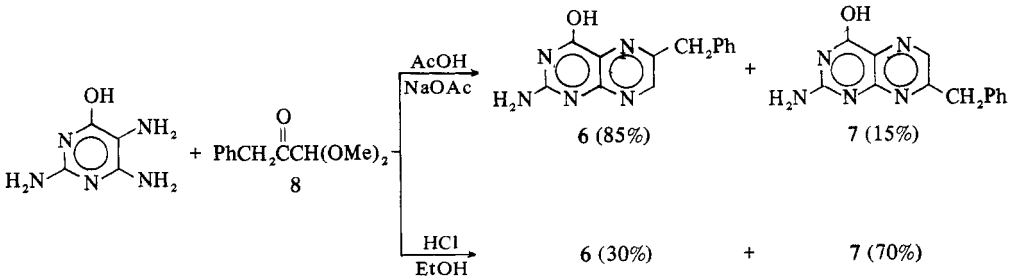
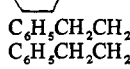
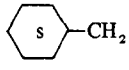


Table I. 6,7-Disubstituted Pteridines

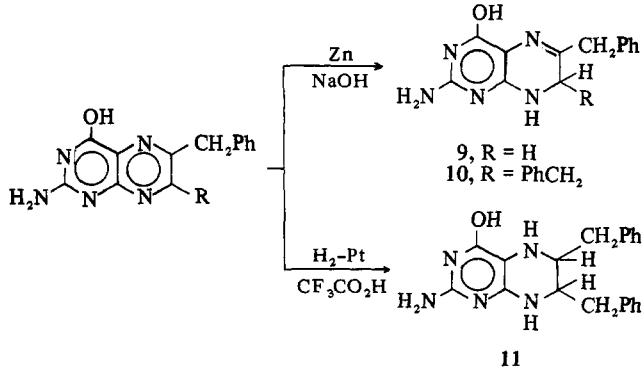
Compd	R	Procedure[a]	Yield, %	Mp, °C	Recrystn solvent	Empirical formula	Analyses
1a	4-$ClC_6H_4CH_2$	A	37	231-234	95% EtOH	$C_{20}H_{16}Cl_2N_6$	C, H, Cl, N
1b	3,4-$Cl_2C_6H_3CH_2$	A	43	249-256	95% EtOH	$C_{20}H_{14}Cl_4N_6$	C, H, Cl, N
1c	3,4-$Me_2C_6H_3CH_2$	B	70	244-248	MeOH	$C_{24}H_{26}N_6 \cdot 2H_2O$	C; H[b]
1d	3-$CF_3C_6H_4CH_2$	C	56	244-247	50% HCO_2H	$C_{22}H_{16}F_6N_6$	C, H, F, N
1e	4-*n*-$BuC_6H_4CH_2$	C	45	234-238	70% HCO_2H	$C_{28}H_{34}N_6 \cdot HCO_2H \cdot H_2O$	C, H, N
1f	2-$C_{10}H_7CH_2$	C	65	252-261	60% HCO_2H	$C_{28}H_{22}N_6 \cdot {}^4/_3H_2O$	C, H, N
1g		A	33	267-274[c]	AcOH-H_2O	$C_{20}H_{30}N_6 \cdot H_2O$	C, H, N
1h	$C_6H_5CH_2CH_2$	A	58	216-218	90% EtOH	$C_{22}H_{22}N_6$	C, H, N
1i	$C_6H_5CH_2CH_2CH_2$	A	67	146-149 181-183[d]	95% EtOH	$C_{24}H_{26}N_6 \cdot 0.5H_2O$	C, H, N
2a	$C_6H_5CH_2$	C	39	338-340	80% HCO_2H + H_2O[e]	$C_{20}H_{17}N_5O \cdot 0.75H_2O$	C, H, N
2b	4-$ClC_6H_4CH_2$	C	39	337-340	80% HCO_2H	$C_{20}H_{15}Cl_2N_5O$	C, H, Cl, N
2c	3,4-$Cl_2C_6H_3CH_2$	C	65	338-340	80% HCO_2H + H_2O[e]	$C_{20}H_{13}Cl_4N_5O$	C, H, Cl, N
2d	3,4-$Me_2C_6H_3CH_2$	C	45	319-323	80% HCO_2H	$C_{24}H_{25}N_5O$	C, H, N
2e	3-$CF_3C_6H_4CH_2$	C	44	318-321	70% HCO_2H + H_2O[e]	$C_{22}H_{15}F_6N_5O$	C, H, F, N
2f	4-*n*-$BuC_6H_4CH_2$	C	48	338-343	80% HCO_2H	$C_{28}H_{33}N_5O$	C, H, N
2g	2-$C_{10}H_7CH_2$	C	64	287-290	90% HCO_2H	$C_{28}H_{21}N_5O \cdot HCO_2H$	C, H, N
2h	3,4-$(CH_2O_2)C_6H_3CH_2$	C	58	298-301	DMF-H_2O	$C_{22}H_{17}N_5O_5$	C, H, N
2i		A	41	>350	70% HCO_2H	$C_{20}H_{29}N_5O$	C, H, N
2j	$C_6H_5CH_2CH_2$	A	58	269-284	75% HCO_2H	$C_{22}H_{21}N_5O \cdot 0.5H_2O$	C, H, N
2k	$C_6H_5CH_2CH_2CH_2$	A	74	324-332	70% HCO_2H + H_2O[e]	$C_{24}H_{25}N_5O$	C, H, N
2l	$-(CH_2)_{10}-$	A	21	>360	80% HCO_2H + H_2O[e]	$C_{16}H_{23}N_5O$	C; H[f]
5a	4-ClC_6H_4	D	62	260-263	80% HCO_2H	$C_{20}H_{13}Cl_2N_5O_3S$	C, H, Cl; S[g]
5b	3,4-$Cl_2C_6H_3$	D	63	270-275	60% HCO_2H	$C_{20}H_{11}Cl_4N_5O_3S$	C, H, Cl, N, S
5c	3,4-$Me_2C_6H_3$	D	48	244-250	70% HCO_2H	$C_{24}H_{23}N_5O_3S$	C, H, N, S
5d	3-$CF_3C_6H_4$	D	54	228-235	EtOH-MeOH	$C_{21}H_{13}F_6N_5O_3S$	C, H, F, N, S
5e	4-*n*-BuC_6H_4	D	43	195-208	80% HCO_2H + H_2O[e]	$C_{28}H_{31}N_5O_3S$	C, H, N, S
5f	2-$C_{10}H_7$	D	60	270-280	80% HCO_2H + H_2O[e]	$C_{28}H_{19}N_5O_3S \cdot 0.5HCO_2H$	C, H, N, S
5g	3,4-$(CH_2O_2)C_6H_3$	D	18	272-300	DMF-H_2O	$C_{22}H_{15}N_5O_7S \cdot H_2O$	C, H, N, S

[a] A, preparation of pteridines from α-diketones; B, preparation of pteridines from tetrahydrothiophen-4-ol-3-one dioxides; C, preparation of pteridines from dihydrothiophen-4-ol-3-one dioxides; D, preparation of thieno[3,4-*g*]pteridines from dihydrothiophen-4-ol-3-one dioxides. [b] N: calcd, 19.34; found, 18.91. [c] Lit.[3] mp 230°. [d] Double melting point. [e] Crystallization was effected by dilution of an aqueous HCO_2H solution with H_2O. [f] N: calcd, 23.23; found, 22.80. [g] N: calcd, 14.76; found, 14.26.

enediamines.[44,45] Unfortunately, however, in contrast to the facile reductive dethiation reported for thieno[3,4-*g*]-quinoxalines,[44,45] trial experiments using Davison sponge nickel failed to convert the tricyclic sulfones **5** into the pteridines **2**.

The heretofore unreported 2-amino-6-benzyl-4-hydroxypteridine (**6**) and its 7-benzyl isomer, **7**, were prepared from 2,4,5-triamino-6-hydroxypyrimidine and 1,1-dimethoxy-3-phenyl-2-propanone (**8**). The latter was obtained readily from *N*-(dimethoxyacetyl)piperidine and benzylmagnesium chloride as reported in the literature.[46,47] When the condensation of **8** with 2,4,5-triamino-6-hydroxypyrimidine was carried out in glacial AcOH in the presence of NaOAc, the principal product (85%) was pteridine **6** and the minor product (15%) was **7**. If 4 *N* HCl in EtOH was used in place of AcOH-NaOAc, on the other hand, the expected[48] preponderant product (70%) was **7**. In each instance, the mixture of pteridines was purified by repeated digestion with boiling glacial AcOH and the homogeneity of the product was determined by nmr analysis in 4:1 CF_3CO_2H-FSO_3H solution, a technique which allows 6- and 7-monosubstituted 2-amino-4-hydroxypteridines to be differentiated unequivocally.[1,49]

The 7,8-dihydro derivatives **9** and **10** were prepared by reduction of 2-amino-6,7-dibenzyl-4-hydroxypteridine (**1**, R = $PhCH_2$) and **6**, respectively, with metallic Zn in 0.5 *N* NaOH. Tetrahydro derivative **11** was obtained by catalytic hydrogenation over PtO_2 in CF_3CO_2H solution. All three reduced pteridines were isolated in stable crystalline form as solvated HCl salts. The structures of **9** and **10** were verified on the basis of nmr spectra in CF_3CO_2H solution. Compound **9** showed the 6-$PhCH_2$ and N-CH_2 methylene protons as singlets at δ 4.18 and 4.87, respectively. Compound **10** showed the 6-$PhCH_2$ methylene as a quartet at δ 4.22 (J = 8 Hz), the 7-$PhCH_2$ methylene as a doublet at δ 3.06 (J = 6 Hz), and the C-7 methine proton as a multiplet at δ 5.14. In accord with these assignments, the 5,6,7,8-tetrahydro derivative **11** showed the benzylic methylenes as a multiplet at δ 3.15 and the methine protons as a multiplet at δ 4.30. The multiplicity displayed by the benzylic proton signals in **10** and **11** is indicative of magnetic nonequivalence due to sterically hindered rotation.



Biological Results. All the pteridines synthesized in this work, as well as several which we have reported separately,[1] were assayed for growth-inhibitory activity against *Streptococcus faecium* (ATCC No. 8043) by the method of Foley

Table II. Inhibition of *S. faecium* (ATCC No. 8043) by Selected 2,4-Diaminopteridines

Compd	ID_{50}, μg/ml[a]	Compd	ID_{50}, μg/ml[a]
1a	0.02	1f	0.02
1b	0.02	1g	0.02
1c	0.001	1h	0.3
1e	1.0	1i	0.03

[a] Folate = 0.001 μg/ml.

and coworkers.[50] In the presence of 0.001 μg/ml of folate, this organism was inhibited significantly by the 2,4-diaminopteridines but not the 2-amino-4-hydroxypteridines. Selected data for the former compounds are presented in Table II. The most active member of the series, 1c (1, R = 3,4-$Me_2C_6H_3CH_2$), had an ID_{50} value of 0.001 μg/ml. 2,4-Diamino-6,7-dibenzylpteridine (1, R = $C_6H_5CH_2$)[3] had previously been found to have an ID_{50} value of 0.09 μg/ml in the same test system.‡ Thus, the introduction of two extra Me groups in each aromatic ring resulted in approximately a 100-fold increase in activity against this particular microorganism. A similar, although smaller improvement was also brought about by using 2-naphthylmethyl or cyclohexylmethyl groups (1f, 1g). The use of 4-*n*-butylbenzyl groups (1e), on the other hand, proved to be detrimental. Interposition of a second methylene group between the phenyl and pteridine moieties (1h) led to a small decrease in activity, whereas extension of the bridge length to three methylenes (1j) had the opposite effect. In general, it appears that no very large gain in activity can be realized in this series by altering the hydrophobic character of the 6,7-bis(aralkyl) groups. A similar conclusion may be drawn from recently published data for a series of 2,4-diamino-6-(2-phenylethyl)pteridines.[40]

Antimalarial evaluation of the compounds synthesized in this program was carried out under the auspices of the Walter Reed Army Institute of Research. Standard assays against *Plasmodium berghei* in the mouse and *Plasmodium gallinaceum* in the chick were performed according to the procedure of Rane and coworkers.[51] 2,4-Diamino-6,7-bis(cyclohexylmethyl)pteridine (1g) afforded a marginal extension of survival in mice infected with *P. berghei* (Table III) but was the only 2,4-diaminopteridine showing activity in this system. Thus, despite the potent antimalarial properties of 2,4-diaminopteridines of the triamterene type,[51,52] the results of this study reinforce the impression of many other investigators that *S. faecium* data, no matter how encouraging, cannot necessarily be translated into antimalarial activity in higher animals.

Somewhat unexpectedly, borderline activity was shown against *P. berghei* in the mouse by the previously described 2-amino-4-hydroxy-6-*n*-nonylpteridine[1] and 2-amino-4-hydroxy-6-(3-phenylpropyl)pteridine[1,41] and also by 2-amino-7-benzyl-4-hydroxypteridine (7). Although not of a high order, the activity of these 6- (and 7-) monosubstituted 2-amino-4-hydroxypteridines is nonetheless of considerable interest. Since there is no parallel activity in the *S. faecium* assay, it appears that these compounds do not inhibit dihydrofolate reductase. The possibility exists that they may act as inhibitors of another tetrahydrofolate-linked enzyme, such as thymidylate synthetase, after reduction *in vivo* to the tetrahydro form. Another reduced 2-amino-4-hydroxypteridine derivative, tetrahydrohomopteroic acid, has been shown to have significant experimental antimalarial activity against both pyrimethamine-sensitive and pyrimethamine-resistant strains of *Plasmodium cynomolgi* in monkeys,[27,28] and tetrahydrohomofolate is known to inhibit thymidylate synthetase in *Escherichia coli*[53] and to interfere with folate uptake in *S. faecium*.[54] Although initial efforts to take advantage of these observations synthetically were unrewarding,[41,55] our results suggest that this approach nonetheless merits further investigation.§

‡S. Tishler, S. Chatterjee, G. E. Foley, and E. J. Modest, unpublished results.

Table III. Antimalarial Evaluation of Selected 2-Amino-4-hydroxypteridines against *P. berghei* in Mice

Compd	Dose, mg/kg	Survival, days treated/controls
1g	40	6.4/6.1
	160	7.2/6.1
	640	10.0/6.1
2-Amino-4-hydroxy-6-*n*-nonylpteridine	40	6.4/6.1
	160	6.6/6.1
	640	10.2/6.1
2-Amino-4-hydroxy-6-(3-phenylpropyl)pteridine	40	6.4/6.1
	160	6.6/6.1
	640	12.0/6.1
7	40	6.4/6.1
	160	6.6/6.1
	640	11.4/6.1

Pteridines 2c, 5a, 9, 10, and 11 were tested for antineoplastic activity against L1210 ascitic lymphatic leukemia and P1534 lymphatic leukemia (ascitic form) in the mouse. The assay procedure has been described previously.[56] At nontoxic doses, none of these agents showed significant antitumor activity.

Experimental Section#

Bis(3,4-methylenedioxybenzyl) Sulfide. Dry HCl gas was passed through a solution of piperonyl alcohol (100 g, 0.658 mol) in C_6H_6 (100 ml) until the point of saturation was reached (6.5 hr). A small amount of unsoluble material was filtered off and the layers were separated. Drying of the C_6H_6 layer over anhydrous $CaCl_2$ and evaporation under reduced pressure gave piperonyl chloride (108 g, 96% yield) as a pale yellow liquid. A solution of this chloride in EtOH (800 ml) was treated dropwise with a solution of $Na_2S \cdot 3H_2O$ (60% technical flakes, 41.2 g, 0.32 mol) in H_2O (40 ml), and the mixture was stirred under reflux for 5 hr, cooled, and poured into H_2O (1 l.). Overnight refrigeration, filtration of the precipitated solid, and recrystallization from EtOH gave 60.8 g (63.5% yield) of colorless needles, mp 60–62°. *Anal.* ($C_{16}H_{14}O_4S$) C, H.

Bis(3,4-methylenedioxybenzyl) Sulfone. A solution of the foregoing sulfide (49 g, 0.162 mol) in glacial AcOH (400 ml) was treated dropwise at 40° with 30% H_2O_2 (93.5 g, 0.825 mol). The reaction mixture was heated at 60–70° for 4 hr, kept overnight at room temperature, and filtered, and the solid was washed with H_2O and dried: yield 53.1 g (98.2%). Recrystallization from MeCN

§ According to recent results obtained by Dr. Leo Rane at the University of Miami and provided to us through the courtesy of Dr. Edgar A. Steck (Walter Reed Army Institute of Research), several of the 2-amino-4-hydroxypteridines reported here, including 2i and 7, display promising prophylactic activity in the sporozoite-induced *P. gallinaceum* chick assay. Since this test does not, by itself, permit true causal prophylaxis to be distinguished from suppressive prophylaxis, additional experiments must be performed before the mode of action of these compounds can be elucidated.

Ir spectra were taken with a Perkin-Elmer Model 137B double-beam recording spectrophotomer. Quantitative uv spectra were measured on Cary Model 11 and 15 spectrophotometers. Nmr spectra were determined on a Varian A-60 instrument, with CF_3CO_2H or 4:1 CF_3CO_2H–FSO_3H as the solvent and Me_4Si as the reference. With the latter solvent a sealed capillary tube containing Me_4Si was placed in the nmr sample tube. Melting points were measured in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.) and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Werby Laboratories, Boston, Mass. Where analyses are indicated only by a symbol of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

(charcoal) yielded colorless prisms, mp 218–220°. *Anal.* ($C_{16}H_{14}O_6S$) C, H, S.

Bis(4-*n*-butylbenzyl) Sulfone. A solution of $Na_2S \cdot 3H_2O$ (60% technical flakes, 40 g, 0.303 mol) in H_2O (50 ml) was added slowly over a period of 30 min to a solution of 4-*n*-butylbenzyl chloride (112 g, 0.613 mol)[57] in EtOH (180 ml). After being refluxed for 18 hr, the solution was poured into a large volume of H_2O. Extraction with Et_2O, drying, and solvent evaporation gave the sulfide as a colorless oil (90 g, 90%). This was dissolved directly in glacial AcOH (450 ml) and the solution was heated at 80–90° while 30% H_2O_2 (113 g, 1.0 mol) was added slowly over a period of 45 min. After being kept at 80° for 3 hr, the mixture was cooled and diluted with H_2O (500 ml). The precipitated solid was filtered, washed with H_2O, and dried: yield 90 g (90% overall). Recrystallization from EtOH gave colorless needles, mp 158–159°. *Anal.* ($C_{22}H_{30}O_2S$) C, H, S.

2,3-Dihydro-2,5-bis(3,4-methylenedioxyphenyl)thiophen-4-ol-3-one 1,1-Dioxide (3, Ar = 3,4-Methylenedioxyphenyl). To a stirred solution of NaOEt (from 0.98 g of Na metal) in absolute EtOH (50 ml) were added successively bis(3,4-methylenedioxybenzyl) sulfone (6.5 g, 0.0194 mol) and diethyl oxalate (19.8 g, 0.136 mol). The mixture was heated to reflux for 7 hr and then stirred at room temperature overnight. Et_2O (150 ml) was added, and the precipitated yellow solid was filtered, washed thoroughly with Et_2O, and suspended in H_2O (300 ml). The insoluble portion was filtered off, the filtrate was acidified with concentrated HCl, and the resulting gummy solid was separated from the aqueous phase and caused to crystallize by trituration with EtOH: yield 5.5 g (73.3%); mp 239–241° dec (MeCN). *Anal.* ($C_{18}H_{12}O_8S$) C, H, S.

2,5-Bis(4-*n*-butylphenyl)-2,3-dihydrothiophen-4-ol-3-one 1,1-Dioxide (3, Ar = 4-*n*-BuC_6H_4). To a stirred solution of NaOEt (from 5.15 g, 0.224 g-atom of Na metal) in absolute EtOH (265 ml) were added successively bis(4-*n*-butylbenzyl) sulfone (37 g, 0.102 mol) and diethyl oxalate (74.5 g, 0.51 mol). After being heated under reflux for 4 hr, the mixture was poured into H_2O (1200 ml). The pH was adjusted to 9 with NaOH, the insoluble material was filtered off, the filtrate was acidified with concentrated HCl, and the precipitated solid was collected, washed with H_2O, and dried: yield 39.6 g (94.1%); mp 218–219° (C_6H_6). *Anal.* ($C_{24}H_{28}O_4S$) C, H, S.

1,8-Diphenyl-4,5-octanedione. To a rapidly stirred mixture of finely powdered Na metal (40% dispersion in mineral oil, 39.7 g, 0.69 g-atom) and dry Et_2O (120 ml) was added dropwise over a 1-hr period a solution of methyl 4-phenylbutyrate (60 g, 0.33 mol) in Et_2O (60 ml). After being refluxed for 2. 5 hr, the mixture was cooled in an ice bath, and excess Na was destroyed by addition of EtOH (10 ml) followed by 60% aqueous H_2SO_4 (160 ml). After filtration through Celite and washing of the filter cake with Et_2O, the combined filtrate and wash solution were rinsed with H_2O, saturated $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The resultant mixture of 1,8-diphenyloctan-4-ol-5-one and mineral oil (66.6 g) was added directly to a stirred mixture of $Cu(OAc)_2 \cdot H_2O$ (63.5 g, 0.318 mol), 50% AcOH (240 ml), and MeOH (75 ml). After being refluxed for 40 min, during which time a dark purple color appeared, the mixture was filtered through Celite, the filter pad was washed with Et_2O, and the combined filtrate and wash solution were washed successively with H_2O, 10% $NaHCO_3$, H_2O, and saturated NaCl. Drying (Na_2SO_4) and solvent evaporation yielded a yellow oil which crystallized on addition of small amounts of *i*-Pr_2O and EtOH at 0°. Recrystallization of the product (14.3 g, 29.4%) from EtOH afforded greenish-yellow platelets, mp 70–71.5°. *Anal.* ($C_{20}H_{22}O_2$) C, H.

Preparation of Pteridines from α-Diketones (Procedure A). 2,4-Diamino-6,7-bis(3,4-dichlorobenzyl)pteridine (1b). A mixture of 2,4,5,6-tetraaminopyrimidine sulfate (2.38 g, 0.01 mol), MeOH (150 ml), and H_2O (72 ml) was warmed gently and neutralized to pH 7 with Na_2CO_3 (1.35 g, 0.0127 mol). After 15 min, the mixture was acidified to pH 6 with glacial AcOH and 1,4-bis(3,4-dichlorophenyl)-2,3-butanedione (4.8 g, 0.0128 mol)[37] was added. The mixture was stirred under reflux for 5 hr and then at room temperature overnight. The solid was filtered, washed with H_2O, and digested with boiling 95% EtOH (2400 ml). The insoluble portion (1.2 g) was removed and the filtrate was concentrated to a small volume until crystallization occurred, giving yellow prisms (2.6 g, 42.6%).

2-Amino-4-hydroxy-6,7-bis(3-phenylpropyl)pteridine (2k). A mixture of 1,8-diphenyl-4,5-octanedione (5.0 g, 0.0169 mol), 2,4,5-triamino-6-hydroxypyrimidine sulfate (4.35 g, 0.0169 mol), Na_2CO_3 (1.79 g, 0.0169 mol), glacial AcOH (30 ml), MeOH (400 ml), and H_2O (15 ml) was stirred under reflux for 4 hr, cooled, and filtered. The solid was dissolved in hot 70% HCO_2H and H_2O was added dropwise with cooling until crystallization occurred (5 g, 74%).

2-Amino-4-hydroxy-6,7-decamethylenepteridine (2l). A stirred mixture of cyclododecanone (18.4 g, 0.101 mol), AcCl (3 ml), and dry C_6H_6 (60 ml) was warmed to 55–60°, and a solution of *n*-BuONO (11.5 g, 0.112 mol) in C_6H_6 (20 ml) was added dropwise over a 1-hr period. The mixture was then cooled to room temperature, treated with 40% NaOH (100 ml), stirred vigorously for 15 min, diluted with H_2O (600 ml), and transferred to a separatory funnel. The aqueous layer was separated, cooled in an ice bath, acidified dropwise with dilute H_2SO_4, and extracted with Et_2O (600 ml). The Et_2O extract was washed with H_2O, dried, and evaporated under reduced pressure. The thick oily residue (13.5 g) was added, without further purification, to a mixture of 37% formalin (103 ml), H_2O (103 ml), and concentrated HCl (52 ml) which was then heated on a steam bath for 35 min with occasional shaking, cooled, and extracted with Et_2O (300 ml). The Et_2O solution was washed with H_2O, dried, and evaporated to a thick oil which solidified on storage at 0° (10.8 g, 54.5% overall yield). A mixture of 2,4,5-triamino-6-hydroxypyrimidine sulfate (14.2 g, 0.0553 mol) and $BaCl_2$ (13.5 g, 0.065 mol) in H_2O (166 ml) was warmed on a steam bath for 15 min and filtered through Celite. To the filtrate were added immediately a solution of the foregoing oil and NaOAc (4.42 g, 0.054 mol) in EtOH (30 ml). The mixture was stirred at room temperature for 3 hr, then warmed on the steam bath for 2 hr, and finally cooled and filtered. The solid was washed with H_2O, warm EtOH, and Et_2O: yield 3.43 g (20.7%).

Preparation of Pteridines from Tetrahydrothiophen-4-ol-3-one Dioxides (Procedure B). 2,4-Diamino-6,7-bis(3,4-dimethylbenzyl)-pteridine (1c). A stirred mixture of 2,4,5,6-tetraaminopyrimidine sulfate (2.38 g, 0.01 mol), MeOH (150 ml), and H_2O (50 ml) was made slightly basic with Na_2CO_3 (1.06 g, 0.01 mol). After 10 min, the mixture was acidified to pH 6 with glacial AcOH and 2,3,4,5-tetrahydro-2,5-bis(3,4-dimethylphenyl)thiophen-4-ol-3-one 1,1-dioxide (4, Ar = 3,4-$Me_2C_6H_3$, 3.58 g, 0.01 mol) was added. The mixture was stirred under reflux for 7 hr and then at room temperature overnight, and the solid was filtered and digested with boiling MeOH (400 ml). Filtration of the insoluble portion (0.3 g) and overnight refrigeration at 0° gave pale yellow needles (2.8 g, 70%).

Preparation of Pteridines from Dihydrothiophen-4-ol-3-one Dioxides (Procedure C). 2,4-Diamino-6,7-bis(2-naphthylmethyl)-pteridine (2g). A mixture of 2,3-dihydro-2,5-bis(2-naphthyl)-thiophen-4-ol-3-one 1,1-dioxide (3, Ar = 2-$C_{10}H_7$, 8 g, 0.02 mol), glacial AcOH (160 ml), THF (320 ml), and absolute EtOH (80 ml) was cooled to 6°, and Zn dust (6.54 g, 0.1 g-atom) was added with stirring. After 75 min, during which time the temperature rose gradually to 14° and the color turned from yellow to grey, the mixture was filtered, and the filter cake was washed thoroughly with EtOH. The combined filtrate and wash solution were concentrated to dryness, and the yellow residue was transferred to a flask containing 2,4,5,6-tetraaminopyrimidine sulfate (5.76 g, 0.02 mol), Na_2CO_3 (2.12 g, 0.02 mol), MeOH (400 ml), and H_2O (40 ml). After being stirred under reflux for 8 hr and kept at room temperature overnight, the mixture was filtered, and the solid was washed with H_2O and recrystallized from 60% HCO_2H (charcoal) in the form of pale yellow microcrystals (5.78 g, 65.4%).

2-Amino-6,7-bis(3-trifluoromethylbenzyl)-4-hydroxypteridine (2e). Powdered Zn (3.25 g, 0.05 g-atom) was added portionwise at 2.5° to a stirred mixture of 2,5-bis(3-trifluoromethylphenyl)-2,3-dihydrothiophen-4-ol-3-one 1,1-dioxide (3, Ar = 3-$CF_3C_6H_4$, 4.36 g, 0.01 mol), glacial AcOH (30 ml), THF (30 ml), and absolute EtOH (30 ml). The temperature was raised to 7° and after 13 min the mixture, which had now turned from greenish-yellow to grey, was filtered. The solid was washed with EtOH and the combined filtrate and wash solution were reduced to half-volume and added to a slurry of 2,4,5-triamino-6-hydroxypyrimidine sulfate (2.57 g, 0.01 mol) and Na_2CO_3 (1.06 g, 0.01 mol) in MeOH (50 ml) and H_2O (15 ml). The mixture was stirred under reflux for 4 hr and then kept at room temperature overnight. The solid was filtered and redissolved in hot 70% HCO_2H (100 ml). Addition of H_2O (8 ml) and cooling at 0° yielded 2e as an off-white powder (2.1 g, 43.8%).

Preparation of Thieno[3,4-*g*]pteridines (Procedure D). 2-Amino-6,8-bis(4-chlorophenyl)-6,8-dihydro-4-hydroxythieno[3,4-*g*]-pteridine 7,7-Dioxide (5a). A mixture of 2,5-bis(4-chlorophenyl)-2,3-dihydrothiophen-4-ol-3-one 1,1-dioxide (3, Ar = 4-ClC_6H_4, 3.69 g, 0.01 mol),[37] 2,4,5-triamino-6-hydroxypyrimidine sulfate (2.57 g, 0.01 mol), Na_2CO_3 (1.3 g, 0.012 mol), glacial AcOH (20 ml), and MeOH (70 ml) was stirred under reflux for 4 hr. After being filtered, washed with H_2O, and dried, the crude product (4.5 g) was recrystallized from 80% HCO_2H in the form of a bright yellow powder (2.92 g, 61.6%).

2-Amino-6-benzyl-4-hydroxypteridine (6). A mixture of 2,4,5-

triamino-6-hydroxypyrimidine sulfate (7.7 g, 0.03 mol), 8 (6.7 g, 0.03 mol),[46,47] and NaOAc (4.9 g, 0.06 mol) in glacial AcOH (200 ml) was refluxed for 1 hr, diluted with H_2O (50 ml), and refluxed for another 30 min. The mixture was cooled and the precipitate was collected and washed with AcOH, H_2O, and EtOH. The resulting tan solid (6.2 g) was boiled with AcOH (400 ml) and filtered, and the process was repeated twice more to give **6** (3.5 g, 46.2%) as a light tan solid: mp >360°; nmr (4:1 CF_3CO_2H–FSO_3H) δ 4.78 (s, CH_2), 9.4 (s, 7-CH). *Anal.* ($C_{13}H_{11}N_5O$) C, H, N.

2-Amino-7-benzyl-4-hydroxypteridine (7). A mixture of 2,4,5-triamino-6-hydroxypyrimidine sulfate (5.14 g, 0.02 mol) and **8** (4.44 g, 0.02 mol)[46,47] in 4 *N* HCl (120 ml) and EtOH (80 ml) was refluxed for 1.5 hr. The solution was cooled, the pH was adjusted to 4 with concentrated NaOH, and the precipitated solid was filtered and washed with H_2O, EtOH, and Et_2O. The resulting yellow solid (4.4 g) was digested with boiling AcOH as in the preceding experiment to give 1.55 g (30.6%) of **7**, contaminated with a trace (<4% by nmr) of **6**: mp >360°; nmr (4:1 CF_3CO_2H–FSO_3H) δ 4.64 (s, CH_2), 8.8 (s, 6-CH). *Anal.* ($C_{13}H_{11}N_5O$) C, H, N.

2-Amino-6-benzyl-7,8-dihydro-4-hydroxypteridine Hydrochloride (9·HCl). A solution of **6** (4.0 g, 0.016 mol) in 0.5 *N* NaOH (150 ml) was heated to 90° and stirred while powdered Zn metal (20 g, 0.65 g atom) was added in one portion. After 20 min at 90° the hot mixture was filtered through Celite and the filtrate was acidified with concentrated HCl (25 ml). Refrigeration gave **9**·HCl as yellow needles (4.0 g, 84%): mp 200–205° (charring); nmr (CF_3CO_2H) δ 4.18 (s, $=CCH_2$), 4.87 (s, CH_2N); uv (0.1 *N* HCl) 254 nm (ε 15,820), 335 (4830), 370 (3910). *Anal.* ($C_{13}H_{13}N_5O\cdot HCl\cdot 0.5H_2O$) C, H, Cl, N.

2-Amino-6,7-dibenzyl-7,8-dihydro-4-hydroxypteridine Hydrochloride (10·HCl). Reduction of **2a** as described in the preceding experiment afforded a 78% yield of yellow needles: mp 217–222° dec; nmr (CF_3CO_2H) δ 3.06 (d, CH_2), 4.22 (q, $=CCH_2$), 5.14 (m, CH); uv (0.1 *N* HCl) 258 nm (ε 14,995), 367.5 (6340). *Anal.* ($C_{20}H_{19}N_5O\cdot HCl\cdot H_2O$) C, H, Cl, N.

2-Amino-6,7-dibenzyl-5,6,7,8-tetrahydro-4-hydroxypteridine Hydrochloride (11·HCl). PtO_2 (400 mg) in CF_3CO_2H (40 ml) was prereduced at room temperature in a Parr apparatus at 23 psi for 20 min. Compound **2a** was added and hydrogenation was carried out at 23 psi for 25 min. The catalyst was filtered and a mixture of 6 *N* HCl (10 ml) and EtOH (50 ml) was added immediately to the filtrate. Evaporation under reduced pressure left a viscous glassy solid which was recrystallized from EtOH (50 ml) to give 1.68 g (64%) of white solid: mp 198–202° dec; nmr (CF_3CO_2H) δ 3.15 (m, CH_2), 4.30 (m, CH). *Anal.* ($C_{20}H_{21}N_5O\cdot HCl\cdot C_2H_5OH\cdot 0.5H_2O$) C, H, Cl, N.

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2-Substituted Cinchoninic Acids as Intermediates in Quinolinemethanol Syntheses†

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The synthesis of six 2-substituted 4-quinolinemethanols *via* 4-hydroxyquinolines and cinchoninic acids as intermediates is described. A new synthetic scheme has been developed which proceeds from two readily available types of starting materials, substituted anilines and carboxylic acids, making possible the production of 4-quinolinemethanols bearing a wide variety of substituents in the 2, 6, and 8 positions. The present examples contain *tert*-butyl and 1-adamantyl groups in the 2 position. Five of the compounds showed antimalarial activity against *Plasmodium berghei*; the most active compound was α-di-*n*-butylaminomethyl-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol.

Discussion

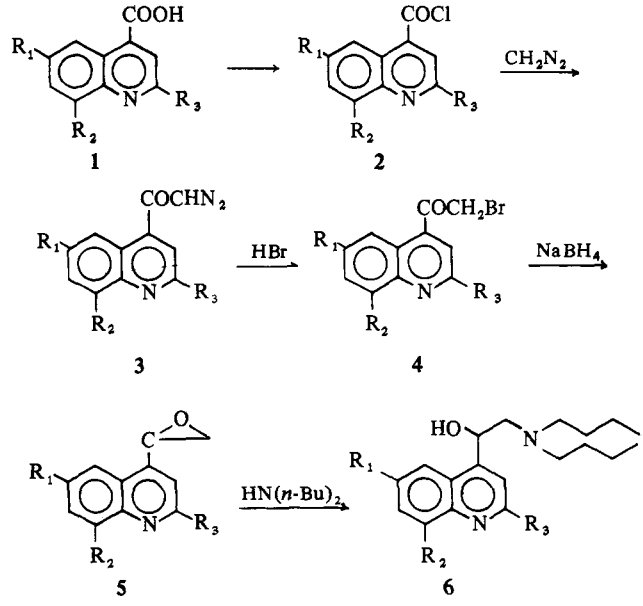
In recent years, the field of 4-quinolinemethanol antimalarials has been extensively researched with respect to the preparation of new compounds of this class. We wish to present our own findings in this area and to report an improved synthesis of 2-substituted cinchoninic acids, which are key intermediates in 4-quinolinemethanol preparation.

The importance of providing the 2 position of the quinoline nucleus with a stable substituent has been emphasized by Lutz,[1] Mead,[2] Schaefer,[3] and Boykin[4] and their coworkers. Consequently, those reactions which yield a 2-substituted quinoline nucleus, such as the Pfitzinger Synthesis,[5] have been frequently employed by a number of investigators in the quinolinemethanol field.[1,6-10],‡ In this connection, a number of 2-aryl-4-quinolinemethanols have been prepared[1,6-11] and while significant antimalarial activity has been demonstrated, the problem of phototoxicity[3,12-15] has precluded their significant utilization as antimalarial agents. Consequently, recent efforts in this field have been directed toward the preparation of quinolinemethanols bearing other than aryl groups in the 2 position. The use of the 2-trifluoromethyl group by Ohnmacht[16] is a case in point.

The low phototoxicity and curative properties of α-di-*n*-butylaminomethyl-2-(1-adamantyl)-6,8-dichloroquinolinemethanol§ suggested that the substitution of the quinoline nucleus by a bulky alkyl group at the 2 position might provide a solution to the problem of phototoxicity. In addition to the adamantane structure, the *tert*-butyl group represents a bulky alkyl structure which is relatively inert and has the additional advantage of providing an economical model for preliminary experiments in the adamantyl series.

Since Lutz had worked out a smooth sequence for the preparation of 4-quinolinemethanols from cinchoninic acids[1] (Scheme I), it was our decision to prepare the appropriate 2-substituted cinchoninic acids (**1**) and then to convert these to the corresponding 4-quinolinemethanols (**6**) through application of Lutz's scheme.

Scheme I



1-6	R_1	R_2	R_3
a	CH_3	H	*t*-Bu
b	Cl	H	*t*-Bu
c	NO_2	H	*t*-Bu
d	Cl	Cl	1-Ad
e	H	CF_3	1-Ad
f	Cl	H	1-Ad

While the Pfitzinger synthesis of substituted cinchoninic acids has been shown to work satisfactorily in several instances,[1,7,17] in others it has not worked well at all.§,[18] The lack of success experienced in our laboratory in the Pfitzinger synthesis of 2-(1-adamantyl)-8-trifluoromethylcinchoninic acid is a case in point. In our hands, condensation of 7-trifluoromethylisatin[19] and acetyladamantane never gave 2-(1-adamantyl)-8-trifluoromethylcinchoninic acid in greater than 8% yield.

After several failures, a reaction scheme (Scheme II) based upon the earlier work of Shah and coworkers[20,21] was devised which provided in good yield the desired 2-substituted quinoline nucleus. This scheme has the additional advantage of utilizing readily available starting materials, specifically carboxylic acids and aromatic amines. Consequently, one can foresee a wide variety of 2-substituted cinchoninic acids as being accessible through this scheme.

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‡For a more comprehensive review of the synthesis and structure of quinolinemethanol antimalarials, see ref 9.

§This compound was prepared earlier in our laboratories by Dr. T. Yamamoto and it was tested for antimalarial activity prior to initiation of this work.