solid was collected and dried at 110° to yield **19** (65.0 g), mp 245–250° dec.

1-Benzylideneamino-3-(2-*p*-toluenesulfonyloxyethyl)-2-imidazolidinone (**25**).—Compound **23** (925 g, 3.97 mol) was added to a solution of C_5H_5N (10,280 ml, dried over KOH pellets) containing recrystallized TsCl (758 g, 3.97 mol). The addition required 30 min with the temperature at 0°. The reaction mixture was stored in the refrigerator for 48 hr. The product was collected, washed with H_2O and then with Et_2O, and dried at 60° to yield 955 g, mp 152–155°. The original filtrate was diluted with H_2O (50,000 ml) and cooled for 72 hr. Upon filtration, washing, and drying, an additional 231 g, mp 150–154°, was obtained. The total yield of **25** was 1186 g (77.6%). Recrystallization from $MeNO_2$ gave an analytical sample, mp 153–155°. *Anal.* ($C_{19}H_{21}N_3O_4S$) C, H, N.

1-(2-Ethoxyethyl)-3-[(5-nitrofurfurylidene)amino]-2-imidazolidinone (**14**).—Compound **25** (84.0 g, 0.22 mol) was added in small portions to a solution of abs EtOH (*ca.* 500 ml) and EtONa [prepared by the addition of NaH (10.4 g of 55.6% oil dispersion)]. The mixture was heated at reflux for 3 hr, filtered, and the solvent removed under reduced pressure. The residue was dissolved in aq MeOH and the solution was acidified (pH **1**) with concd HCl. After heating the solution on the steam bath for 10 min, a solution of **3** (30.6 g, 0.216 mol) in MeOH was added. The reaction mixture was heated on the steam bath for 2 hr, chilled in an ice bath, and filtered. The product was dried to yield 40.0 g, mp 138–140°.

1-(2-Iodoethyl)-3-[(5-nitrofurfurylidene)amino]-2-imidazolidinone (**16**).—A mixture of **25** (194 g, 0.5 mol), NaI (75 g, 0.5 mol), and DMF (2500 ml) was heated at 110–140° for 5 hr. The solution was cooled and diluted twofold with ice–H_2O. A brown ppt was collected, washed with H_2O, and dissolved in aq EtOH. The EtOH solution was acidified (pH 1) with concd HCl and heated on the steam bath for 10 min. A solution of **3** (71 g, 0.5 mol) in 95% EtOH was added and the mixture was heated on the steam bath for 1 hr. The reaction mixture was cooled in an ice bath and filtered. The product was dried to yield 45 g of **16**, mp 186–188°.

1-(2-Chloroethyl)-3-[(5-nitrofurfurylidene)amino]-2-imidazolidinone (**15**).—Compound **9** (152 g, 0.57 mol) was added in small portions to $SOCl_2$ (400 ml). The resultant clear solution was heated at reflux for 30 min, cooled in an ice bath, and filtered. The solid was washed with C_6H_6 and the washings were added to the reaction filtrate to give a second crop of crystals. The total yield of **15** was 92.0 g, mp 184–185°.

In a similar manner **10** and **11** were chlorinated to yield **17** and **18**, respectively.

1-Hydroxymethyl-3-[(5-nitrofurfurylidene)amino]-2-imidazolidinone (**8**).—Compound **1** (60.0 g, 0.27 mol) was added to a refluxing solution of 5% aq CH_2O. The mixture was stirred at reflux for 5 min, filtered hot, and then stored in a refrigerator for 2 days. The precipitated orange plates were collected and washed with 1% CH_2O. The material was dried in a desiccator at room temperature to yield 14.4 g of **8**, mp 200° (sinters).

1-[(5-Nitrofurfurylidene)amino]-3-nitroso-2-imidazolidinone (**20**).—A suspension of **1** (112.0 g, 0.5 mol) in glacial AcOH (*ca.* 800 ml.) was stirred at room temperature while $NaNO_2$ (100 g) was added in small portions over a period of 1 hr. The bright orange suspension gradually changed to a bright yellow. The mixture was stirred for another 3 hr and filtered. The crude solid was washed with Et_2O and recrystd from $MeNO_2$ to yield 50.5 g, mp 228–229° dec. A second crop of material was obtained by concentrating the filtrate and cooling to give a total of 88.5 g.

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Antimalarial Sulfilimines and Sulfoximines Related to Diaminodiphenyl Sulfoxide and Sulfone

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A series of sulfilimines I and sulfoximines II related in structure to 4,4′-diaminodiphenyl sulfone and sulfoxide were synthesized and tested for antimalarial activity (Table I). Compound **12** showed some slight activity in mice infected with *Plasmodium berghei*. The testing did not reveal activity in any of the other compounds.

The sulfilimines were prepared from the known sulfides by reaction with various sodium *N*-chloroarene sulfonamides.[1] Sulfilimines unsubstituted on N appear to be hydrolytically unstable;[2] no attempt was made to prepare such compounds.

Experimental Section

Sulfilimines (**1,2,7,8,10,11,13,14,15**) were prepared from the sulfides by treatment with the appropriate sodium *N*-chloroarenesulfonamide.[2] A typical reaction is given below.

***S,S*-Di-*p*-acetylaminophenyl-*N*-benzenesulfonylsulfilimine** (**2**).—Chloramine B (2.67 g, 0.10 mol) in a 2:1 v/v dioxane–H_2O mixture (18 ml) was added all at once to 4,4′-diacetylaminodiphenyl sulfide (3.0 g, 0.10 mol) in a 2:1 v/v dioxane–H_2O (20 ml) mixture. The mixture was heated on a steam bath for 2 hr. The solvents were removed on a rotary evaporator and the residue dissolved in CH_2Cl_2–EtOAc. This solution was extracted with 5% aq NaOH, washed with H_2O, dried (Na_2SO_4), concd, and recrystd from Me_2CO: 3.0 g; 68%; mp 205°.

Sulfilimines (**3,4,5,6,9,12**) were prepared by the deacetylation of the corresponding acetylated sulfilimine. A typical reaction procedure is given below.

***S,S*-Di-*p*-aminophenyl-*N*-benzenesulfonylsulfilamine** (**3**).—*S,S*-Di-*p*-acetylaminophenyl-*N*-benzenesulfonylsulfilimine (**2**) (4.5 g) in 10% EtOH–NaOH (30 ml) was refluxed for 1 hr. The mixture was reduced in volume and poured into ice–water. The solid which pptd was collected by filtration, washed, dried, and recrystd from EtOH: 3.5 g; 94%; mp 197°.

***S*-Methyl-*S*-*p*-acetylaminophenyl-*N*-benzenesulfonylsulfoximine** (**16**).—*S*-Methyl *S*-*p*-acetylaminophenyl-*N*-benzenesulfonylsulfilimine (**8**) (10.0 g, 0.297 mol) was dissolved in dry C_5H_5N (100 ml) and $KMnO_4$ (3.4 g, 0.22 mol) and H_2O (0.2 ml) was added with stirring. After standing for 6 days at room temperature, the C_5H_5N was removed using a rotary evaporator and the residue treated with aq acidified $NaHSO_3$. The pptd white solid was collected by filtration and recrystd from EtOH: 7.5 g; 71%; mp 173°.

***S*-Methyl-*S*-*p*-acetylaminophenyl-*N*-*p*-acetylaminobenzenesulfonylsulfoximine** (**17**).—*S*-Methyl-*S*-*p*-acetylaminophenylsulfoximine (8.0 g, 0.038 mol) was dissolved in dry THF (400 ml). Na (1.0 g, 0.043 g-atom) was added in small portions to the refluxing solution. When no more Na dissolved, the clear solution was decanted into another flask and *p*-acetylaminobenzenesulfonyl chloride (7.0 g, 0.030 mol) was added. The mixture was refluxed for 45 min, cooled, and filtered. The filtrate was reduced in volume and poured into H_2O whereupon a solid precipi-

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TABLE I
SULFILIMINES AND SULFOXIMINES

$$R_1SR_2(NSO_2R_3)$$

Compd	R_1	R_2	R_3	Mp,[a] °C	Formula[b]
1	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	p-$CH_3C_6H_4$	215–217[c]	$C_{23}H_{23}O_4N_3S_2$
2	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	C_6H_5	205[d]	$C_{22}H_{21}O_4N_3S_2$
3	p-$NH_2C_6H_4$	p-$NH_2C_6H_4$	C_6H_5	197[e]	$C_{18}H_{17}O_2N_3S_2$
4	p-$NH_2C_6H_4$	p-$NH_2C_6H_4$	p-$CH_3C_6H_4$	230[e]	$C_{19}H_{19}O_2N_3S_2$
5	p-$NH_2C_6H_4$	CH_3	C_6H_5	167[c]	$C_{13}H_{14}O_2N_2S_2$
6	p-$NH_2C_6H_4$	p-$NH_2C_6H_4$	p-NH_2C_6H	245 dec[e]	$C_{18}H_{18}O_2N_4S_2$
7[f]	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	163[e]	$C_{24}H_{24}O_5N_4S_2 \cdot H_2O$
8	p-$CH_3CONHC_6H_4$	CH_3	C_6H_5	162[g]	$C_{15}H_{16}O_3N_2S_2$
9	p-$NH_2C_6H_4$	CH_3	p-$CH_3C_6H_4$	212 dec[c]	$C_{14}H_{16}O_2N_2S_2$
10	p-$CH_3CONHC_6H_4$	CH_3	p-$CH_3C_6H_4$	185[c]	$C_{16}H_{18}O_3N_2S_2$
11	p-$CH_3CONHC_6H_4$	CH_3	p-$CH_3CONHC_6H_4$	215 dec[d]	$C_{17}H_{19}O_4N_3S_2$
12	p-$NH_2C_6H_4$	CH_3	p-$NH_2C_6H_4$	224 dec[d]	$C_{13}H_{13}O_2N_3S_2$
13	p-$CH_3CONHC_6H_4$	6-(3-Acetylamino-pyridyl	C_6H_5	242[e]	$C_{21}H_{20}O_4N_4S_2$
14	p-$CH_3CONHC_6H_4$	6-(3-Acetylamino)-pyridyl	p-$CH_3C_6H_4$	177[d]	$C_{22}H_{22}O_4N_4S_2$
15	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	C_6H_5	91[h]	$C_{20}H_{18}O_2NS_2$

$$R_1SOR_2(NSO_2R_3)$$

16	p-$CH_3CONHC_6H_4$	CH_3	C_6H_5	173[e]	$C_{15}H_{16}O_4N_2S_2$
17	p-$CH_3CONHC_6H_4$	CH_3	p-$CH_3CONHC_6H_4$	274[e]	$C_{17}H_{17}O_5N_3S_2$

[a] Melting points are uncorrected. [b] All new compounds analyzed satisfactorily for C, H, N, and S. Compounds **14** and **15** are not analyzed for S. [c] From MeOH. [d] From acetone. [e] From EtOH. [f] From MeOH-Me_2CO. [g] From dioxane-H_2O. [h] From $CHCl_3$. [i] Previously prepared: C. W. Todd, J. H. Fletcher, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **65**, 350 (1943).

tated. The solid was recrystd from EtOH: 5.5 g; 43%; mp 274°.

Pharmacology.—All the compounds were screened against *Plasmodium gallinaceum* in mosquitoes (*Aedes aegypti*). All the compounds except **5**, **15**, and **17** were screened against *P. berghei* in mice. Compounds **12** and **15** were also screened against *P. gallinaceum* in chicks. Compound **12** showed slight activity in the mouse test. At a dose level of 320 mg/kg, the mean survival time of the treated mice was 11.6 days and at a dose level of 640 mg/kg, it was 12.8 days. The mean survival time of the control mice was 6.1 days. Compound **1** was assayed for antifolic acid activity in a bacterial system. It gave questionable activity with *Streptococcus fecalis*, but was inactive with *Lactobacillus casei* and *Pediococcus cerevisiae*. None of the other compounds showed any significant activity. All of the tests were carried out by contractors of the Walter Reed Army Institute of Research.

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Synthesis and Antimalarial Activity of 4-Aminobenzo[*b*]-1,5-naphthyridines[1]

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Antimalarial activity has been reported for several aminosubstituted members of the 1,5-naphthyridine[2] and 1,7-naphthyridine[3] families. Much of the rationale for the early synthetic efforts in these series was predicated on the assumption that certain aminonaphthyridines could be regarded as isosteric analogs of both 4- and 8-aminoquinolines—well-known as antimalarial agents.[4]

Although general synthetic pathways to benzo[*b*]-1,5-naphthyridines have been established,[5] no aminosubstituted antimalarial candidates appear to have been prepared or screened. The 3-aminoquinolines, synthetic precursors of this benzonaphthyridine system, are converted by reaction with ethoxymethylenemalonic ester[6] (EMME) into the 3-carbethoxy-4-hydroxy-[*b*]-1,5-naphthyridines which are modified by standard methods (*vide infra*) into 4-chlorobenzo[*b*]-1,5-naphthyridines (**1**). The cycle formation of 3-aminoquinolines and EMME occurs at C-2 of the original quinoline, leading to benzo[*b*]-1,5-naphthyridines and not at C-4 to produce isomeric benzo[*f*]-1,7-naphthyridines.[5]

Since, of several side-chain amines studied in aminoquinolines, the 3-diethylaminomethyl-4-hydroxyanilino derivatives displayed the most impressive activity,[7,8] attempts were made to incorporate it into these benzonaphthyridines by Burckhalter's procedure.[9] 4-(3-*N*,*N*-Diethylaminomethyl-4-hydroxyanilino)benzo-[*b*]-1,5-naphthyridine (**2a**) was successfully prepared from **1a** but similar attempts to aminate **1b** with the

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