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 C₃H₅N (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 H₂O and then with Et₂O, and dried at 60° to yield 955 g, mp 152–155°. The original filtrate was diluted with H₂O (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 MeNO₂ gave an analytical sample, mp 153– 155°. Anal. (C₁₉H₂₁N₃O₄S) 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-H₂O. A brown ppt was collected, washed with H₂O, and dissolved in aq EtOH. The EtOH solution was acidified (pH 1) with concel 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 CH₂O. 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% CH₂O. 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 NaNO₂ (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 Et₂O and recrystd from MeNO₂ 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.

Acknowledgments.—The authors gratefully acknowledge the aid of Mrs. Patricia Curtis, Mr. Frederick Abbott, Mr. Alexander Winterstein, and Mr. Benjamin Stevenson for the preparation of chemical intermediates, and of Mr. Leonard Bird for assistance in the syntheses. Compound 8 was prepared by Mr. Benjamin Stevenson. Mr. Grant Gustin and Mr. Marvin Tefft performed the microanalyses. Microbiologic data were obtained through the assistance of Mr. Patrick Moynihan. Miss Esther Nohle and Mr. Donald Humphrey assisted in obtaining the urinary excretion data.

Antimalarial Sulfilimines and Sulfoximines Related to Diaminodiphenyl

Sulfoxide and Sulfone

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Received January 7, 1970

A series of sulfilimines I and sulfoximines II related in structure to 4.4'-diaminodiphenyl sulfone and sulf-

$\mathrm{NSO}_2\mathrm{R}_3$	$\mathrm{NSO}_2\mathrm{R}_3$
$\mathbf{R_{1SR_{2}}}$	$\mathbf{R_1 SOR_2}$
I	П

oxide 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*-chloro-arenesulfonamide.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 CH₂Cl₂-EtOAc. This solution was extracted with 5% aq NaOH, washed with H₂O, dried (Na₂SO₄), concd, and recrystd from Me₂CO: 3.0 g; 68%; mp 205°.

recrystd from Me₂CO: 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 KMnO₄ (3.4 g, 0.22 mol) and H₂O (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 NaHSO₃. 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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		R	$_{1}\mathrm{SR}_{2}$		
Compd	\mathbf{R}_1	\mathbf{R}_{2}	\mathbf{R}_{3}	$Mp.^{\sigma-\circ}C$	$Formula^{b}$
1	p-CH ₃ CONHC ₆ H ₄	p-CH ₃ CONHC ₆ H ₄	p-CH ₃ C ₆ H ₄	215 – 217	$C_{23}H_{23}O_4N_3S_2$
2	p-CH ₃ CONHC ₆ H ₄	p-CH ₃ CONHC ₆ H ₄	C_6H_{\odot}	205^{d}	$C_{22}H_{21}O_4N_3S_2$
3	p-NH ₂ C ₆ H ₄	p-NH ₂ C ₆ H ₄	C_6H_5	197^{ϵ}	$\mathrm{C_{18}H_{17}O_2N_3S_2}$
4	p-NH ₂ C ₆ H ₄	p-NH ₂ C ₆ H ₄	p-CH ₃ C ₆ H ₄	230^{e}	$C_{19}H_{19}O_2N_3S_2$
.5	p-NH ₂ C ₆ H ₄	CH_{2}	C_6H_5	167°	${ m C}_{13}{ m H}_{14}{ m O}_2{ m N}_2{ m S}_2$
6	p-NH ₂ C ₆ H ₄	p-NH ₂ C ₆ H ₄	p-NH ₂ C ₆ H	$245~{ m dec}^e$	$\mathrm{C}_{18}\mathrm{H}_{18}\mathrm{O}_{2}\mathrm{N}_{4}\mathrm{S}_{2}$
7^{\prime}	p-CH ₃ CONHC ₆ H ₄	p-CH ₃ CONHC ₆ H ₄	p-CH ₃ CONHC ₆ H ₄	163^{e}	$\mathrm{C}_{24}\mathrm{H}_{24}\mathrm{O}_5\mathrm{N}_4\mathrm{S}_2\cdot\mathrm{H}_2\mathrm{O}$
8	p-CH ₃ CONHC ₆ H ₄	CH_3	C_6H_{i}	162^{f}	$\mathrm{C}_{15}\mathrm{H}_{16}\mathrm{O}_3\mathrm{N}_2\mathrm{S}_2$
9	p-NH ₂ C ₆ H ₄	CH_{*}	p-CH ₃ C ₆ H ₄	$212~{ m dec}^r$	$\mathrm{C_{14}H_{16}O_2N_2S_2}$
10	p-CH ₃ CONHC ₆ H ₄	CH.	p-CH ₃ C ₆ H ₄	185^{c}	$C_{16}H_{18}O_{3}N_{2}S_{2}$
11	p-CH ₃ CONHC ₆ H ₄	CH_3	p-CH ₃ CONHC ₆ H ₄	$215~{ m dec}^y$	${ m C_{17}H_{19}O_4N_3S_2}$
12	p -NH $_2$ C $_6$ H $_4$	CH_3	p -NH $_2$ C $_6$ H $_4$	$224~{ m dec}^{g}$	$\mathrm{C}_{13}\mathrm{H}_{15}\mathrm{O}_2\mathrm{N}_3\mathrm{S}_2$
13	p-CH ₃ CONHC ₆ H ₄	6-(3-Acetylamino)- pyridyl	$C_6 \Pi_{\dot{*}}$	242 ^e	$C_{21}H_{20}O_4N_4S_2$
14	p-CH ₃ CONHC ₆ H ₄	6-(3-Acetylamino)- pyridyl	$p ext{-} ext{CH}_3 ext{C}_6 ext{H}_4$	177^d	$C_{22}H_{22}O_4N_4S_5$
15	p-CH ₃ C ₈ H ₄	p-CH ₃ C ₆ H ₄	$C_{6}H_{5}$	91^{h}	$\mathrm{C}_{20}\mathrm{H}_{1\theta}\mathrm{O}_{2}\mathrm{NS}_{2}$
			$\mathrm{NSO}_2\mathrm{R}_3$		
		R	SOR_2		
16	p-CH ₃ CONHC ₆ H ₄	CH_{*}	C_6H_5	173*	$\mathrm{C_{15}H_{16}O_4N_2S_2}$
17	p-CH ₃ CONHC ₆ H ₄	CH_3	p-CH ₃ CONHC ₆ H ₄	274^{e}	$C_{17}H_{17}O_5N_3S_2$

TABLE I SULFILIMINES AND SULFOXIMINES NSO₂R₃

^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-Me₂CO. ^g From dioxane-H₂O. ^b From CHCl₄. ^f 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.

Acknowledgment.—This work was supported by the U. S. Army Medical Research and Development Command under Research Contract No. 49-193-MD-2946. This is Contribution No. 753 from the Army Research Program on Malaria.

Synthesis and Antimalarial Activity of 4-Aminobenzo[b]-1,5-naphthyridines¹

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Received February 6, 1970

Antimalarial activity has been reported for several aminosubstituted members of the 1,5-naphthyridine² and 1,7-naphthyridine³ 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 ester⁶ (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.⁸ 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

 ⁽¹⁾ Supported by Contract DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command. This publication represents contribution No. 773 from the Army Research Program on Malaria.
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