mole) and mercaptoacetic acid gave an unstable oil (50 g) which, when treated with Ac_2O–C_6H_5N yielded, on filtration, a chromatographically homogeneous solid: 1.0 g; mp 268–269°; λ_{max} 6.05, 6.5, 7.66 μ, tentatively identified as anhydro-4-hydroxy-3,5-bis(2-methoxy-5-methyl-4-nitrophenyl)-1,2,3-thiadiazolium hydroxide. *Anal.* ($C_{18}H_{16}N_4O_7S$) C, H, N, S. The filtrate yielded, on treatment with base, anhydro-4-hydroxy-3-(2-methoxy-5-methyl-4-nitrophenyl)-1,2,3-thiadiazolium hydroxide (0.6 g); mp 180–181° (Et_2O–CH_2Cl_2); λ_{max} 6.03, 6.5, 7.65 μ. *Anal.* ($C_{11}H_9N_3O_4S$) C, H, N, S.

Anhydro-4-hydroxy-5-bromo-3-(5-chloro-2,4-dimethoxyphenyl)-1,2,3-thiadiazolium Hydroxide (24). **A.**—A stirred suspension of **22** (5.44 g, 0.02 mole) and N-bromosuccinimide (4.09 g, 0.023 mole) in CCl_4 (200 ml) was heated under reflux for 48 hr. The cooled reaction mixture yielded **24** (3.5 g), melting point unchanged by admixture with material prepared by B (below).

B.—The anhydro compound **22** (0.12 mole) was brominated in glacial AcOH (250 ml) and anhydrous NaOAc (25 g). Recrystallization of the crude product afforded **24** (21 g).

Anhydro-4-hydroxy-5-chloro-3-(5-chloro-2,4-dimethoxyphenyl)-1,2,3-thiadiazolium Hydroxide (25).—The anhydro compound **22** (32.6 g, 0.12 mole) and anhydrous NaOAc (25 g) were suspended in glacial AcOH (250 ml). Cl_2 was added at 20° until solution was complete. After being heated for 30 min at 100°, the reaction was quenched on ice. Addition of 2.5 *N* NaOH to pH 4 precipitated **25** (18.9 g).

Anhydro-4-hydroxy-5-allylthio-3-(*p*-anisyl)-1,2,3-thiadiazolium Hydroxide (4).—The Na salt of anhydro-4-hydroxy-5-mercapto-3-(*p*-anisyl)-1,2,3-thiadiazolium hydroxide[3] [0.14 mole, mp 177–182°. *Anal.* ($C_9H_7N_2O_2SNa$) C, H] was dissolved in DMF (20 ml) and allyl bromide (0.033 mole) was added. After 72 hr at 25° the mixture was quenched on ice, giving **4** (3.0 g).

Anhydro-4-hydroxy-5-benzylthio-3-(*p*-tolyl)-1,2,3-thiadiazolium Hydroxide (1).—Similarly, anhydro-4-hydroxy-5-mercapto-3-(*p*-tolyl)-1,2,3-thiadiazolium hydroxide sodium salt[3] (0.2 mole, mp 173–175°) in DMF (25 ml) with benzyl bromide (0.22 mole) afforded **1** (5.2 g).

Acknowledgment.—The authors express their appreciation to Miss Josephine Chiaini and Messrs. Louis J. Navarro, Norman A. Glidden, and Andrew Popson for their able technical assistance.

Repository Drugs. VI. 4′-[N-(Aralkylidene-, -Benzylidene-, and -Naphthylidene)sulfanilyl]anilides, 4′-{N-[(Dimethylamino)methylene]sulfanilyl}anilides, and Related Sulfanilylanilides with Prolonged Antimalarial and Antileprotic Action[1]

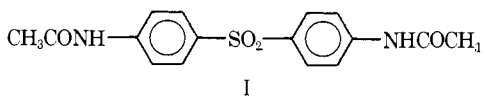
DONALD F. WORTH, EDWARD F. ELSLAGER, AND ANNETTE A. PHILLIPS

Department of Chemistry, Medical and Scientific Affairs Division, Parke, Davis & Company, Ann Arbor, Michigan 48106

Received March 14, 1969

Representative 4′-[N-(aralkylidene-, -benzylidene-, and -naphthylidene)sulfanilyl]anilides (III–VI), N-(aralkylidene- and -benzylidene)-4,4′-sulfonyldianiline derivatives (VII, VIII), and 4′-{N-[(dimethylamino)-methylene]sulfanilyl}anilides (IX) were synthesized as potential repository antimalarial and antileprotic agents in a search for long-acting sulfones that would be less dependent on enzymatic deacylation for activity and afford higher blood sulfone levels than 4′,4‴-sulfonylbisacetanilide (acedapsone, DADDS). The compounds were prepared by condensing the appropriate aldehyde with the requisite 4′-sulfanilylanilides or 4,4′-sulfonyldianiline precursor. Among them, 4′-[N-(benzylidene)sulfanilyl]acetanilide (**3**), 4′-[N-(*p*-acetamidobenzylidene)sulfanilyl]acetanilide (**5**), and 4′-[N-(3,5-dichlorosalicylidene)sulfanilyl]acetanilide (**11**) satisfied the above requirements and showed strong repository activity against *Plasmodium berghei* and *Mycobacterium leprae* in mice. Structure–activity relationships are discussed.

4′,4‴-Sulfonylbisacetanilide (acedapsone, DADDS) (I)[2,3] exhibits strong repository antimalarial activity



I

alone, or in combination with cycloguanil pamoate,[4–6] in experimental animals[2,3,7] and in humans.[8] Further, the drug has protracted action against the human leprosy bacillus *Mycobacterium leprae* in mice[9] and in man.[10]

Inasmuch as DADDS is apparently dependent upon deacetylation for activity and affords only extremely low sulfone blood levels, a repository sulfone that is less dependent on enzymatic deacylation for activity and enables higher blood sulfone levels than DADDS might fulfill a useful need. Therefore, efforts were directed toward the design and synthesis of novel sulfone molecules that might undergo slow, nonenzymatic hydrolytic scission directly upon contact with body tissues and fluids. In a recent communication,[1] we reported the synthesis of certain 4′,4‴-[*p*-phenylene bis-(methylidyneimino-*p*-phenylenesulfonyl)]bisanilides that fulfilled the above requirements and displayed marked repository action. Among them, 4′,4‴-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]-bisformanilide (PSBF) (IIa) was very long acting and protected mice for >9 weeks against challenge with *Plasmodium berghei*.[1] 4′,4‴-[*p*-Phenylenebis(methyli-

(1) Previous paper: E. F. Elslager, A. A. Phillips, and D. F. Worth, *J. Med. Chem.*, **12**, 363 (1969).

(2) E. F. Elslager and D. F. Worth, *Nature*, **206**, 630 (1965). Acedapsone is Hansolar®; Dapolar® is the acedapsone–cycloguanil pamoate combination.

(3) E. F. Elslager, Z. B. Gavrilis, A. A. Phillips, and D. F. Worth, *J. Med. Chem.*, **12**, 357 (1969).

(4) E. F. Elslager and P. E. Thompson, Abstracts, 9th National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minn., June 1964, p 6A.

(5) P. E. Thompson, B. J. Olszewski, E. F. Elslager, and D. F. Worth, *Am. J. Trop. Med. Hyg.*, **12**, 481 (1963).

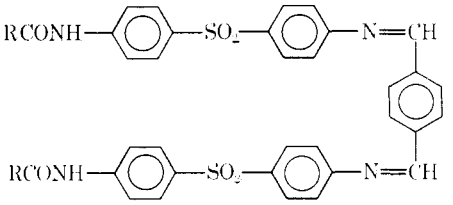
(6) Camolar®.

(7) P. E. Thompson, B. Olszewski, and J. A. Waitz, *Am. J. Trop. Med. Hyg.*, **14**, 343 (1965).

(8) (a) R. H. Black, W. B. Hennessy, B. McMillan, B. B. Dew, and J. C. Biggs, *Med. J. Australia*, **2**, 801 (1966); (b) A. B. G. Laing, G. Pringle, and F. C. T. Lane, *Am. J. Trop. Med. Hyg.*, **15**, 838 (1966); (c) K. H. Rieckmann, *Trans. Roy. Soc. Trop. Med. Hyg.*, **61**, 189 (1967); (d) W. Chin, G. R. Coatney, and H. K. King, *Am. J. Trop. Med. Hyg.*, **16**, 13 (1967); (e) W. Chin, P. G. Contacos, G. R. Coatney, M. H. Jeter, and E. Alpert, *ibid.*, **16**, 580 (1967); (f) D. F. Clyde, Abstracts, 8th International Congresses on Tropical Medicine and Malaria, Teheran, Iran, Sept 7–15, 1968.

(9) C. C. Shepard, *Proc. Soc. Exp. Biol. Med.*, **124**, 430 (1967).

(10) C. C. Shepard, J. G. Tolentino, and D. H. McRae, *Am. J. Trop. Med. Hyg.*, **17**, 192 (1968).



IIa, R = H
b, R = CH$_3$

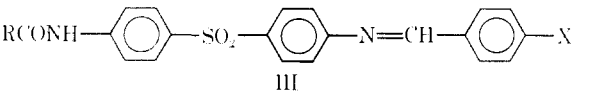
dyneimino-*p*-phenylenesulfonyl)]bisacetanilide (PSBA) (IIb) protected mice against challenge with *P. berghei* for 5–7 weeks, depending on particle size (fine to medium), a period intermediate between the short-acting 4,4′-sulfonyldianiline (DDS) and the very long-acting DADDS.[2,3,7] These results suggested that PSBA should provide higher blood sulfone levels than DADDS and still afford protection for reasonable periods of time.

Expanded repository antimalarial studies with PSBA were carried out utilizing *P. berghei* in rats and *Plasmodium cynomolgi* in monkeys.[1,11,12] A single 400-mg/kg sc dose of PSBA protected rats against challenge with *P. berghei* for 1 week and had strong suppressive action at 5 weeks.[11] It should be recalled that a comparable dose of DADDS in this species failed to provide protection, presumably due in part to the slower rate of mobilization of DADDS at the injection site, and partly because the rat appears to be deficient in enzymes which remove at least one of the acetyl groups from DADDS.[7,11] This presumptive evidence that the scission of PSBA is not enzyme dependent was corroborated by physical-chemical data which showed that PSBA was very labile in aqueous media. In rhesus monkeys, a single 50- or 100-mg/kg im dose of fine particle size PSBA in BBCO protected against challenge with trophozoites of *P. cynomolgi* for an average of 11–13 weeks and greatly suppressed the parasitemia for several weeks longer.[1,12] The mean duration of protection after a single intramuscular 50-mg/kg dose of medium particle size PSBA ranged from 4.4 months in isopropyl myristate–peanut oil (IMPO, 25:75) to 5.1 months in BBCO.[1,12]

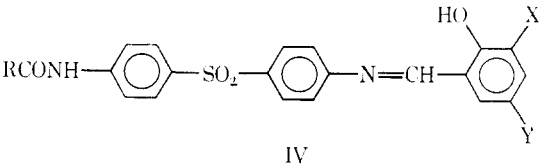
PSBA completely suppressed *M. leprae* infections in mice when administered subcutaneously in a single 200–400-mg/kg dose in BBCO at 2-month intervals.[1,9] The drug also exhibited modest repository activity against *Mycobacterium tuberculosis* $H_{37}Rv$ in mice when given subcutaneously in a single 400–800-mg/kg dose in IMPO.[1]

The present communication summarizes the results of additional studies aimed toward the development of water-labile, respository sulfones whose activation and mobilization from the depot site might not be enzyme dependent. Several of the 4′-[*N*-(benzylidene)sulfanilyl]anilides, 4′-[*N*-(salicylidene)sulfanilyl]anilides, and 4,6-dihalo-α-{[*p*-(*N*-alkylsulfanilyl)phenyl]imino}-*o*-cresols described herein satisfied these requirements and showed promising repository antimalarial and antileprotic activity.

The condensation of the appropriate aldehyde with 4′-sulfanilylformanilide (MFDDS),[3] 4′-sulfanilylacetanilide (MADDS),[3] 4′-sulfanilylheptananilide,[3] or 4′-sulfanilyllauranilide[3] in EtOH, *i*-PrOH, or *i*-AmOH afforded the corresponding 4′-[*N*-(benzylidene)sulfanilyl]anilides (III) (**1–7**, Table I), 4′-[*N*-(salicylidene)-

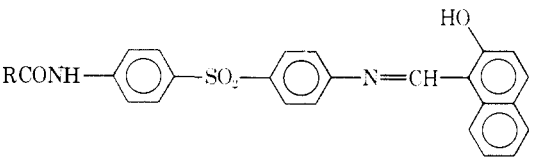


III

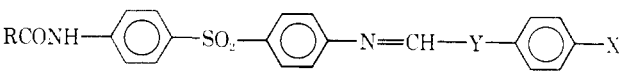


IV

sulfanilyl]anilides (IV) (**8–15**, Table II), 4′-{*N*-[(2-hydroxy-1-naphthyl)methylene]sulfanilyl}anilides (V) (**16–18**, Table III), and 4′-[*N*-(aralkylidene)sulfanilyl]-anilides (VI) (**19–22**, Table IV) in 5–97% yield. Simi-

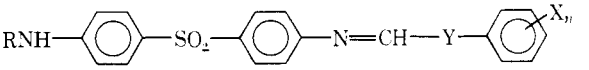


V



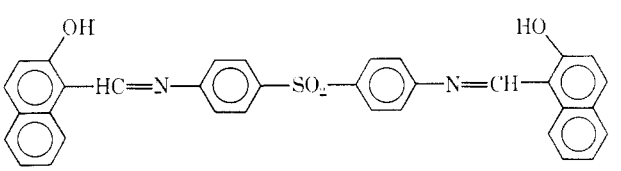
VI

larly, various *N*-(aralkylidene- and -benzylidene)-4,4′-sulfonyldianiline derivatives (VII) (**23–29**, Table V) were prepared from 4,4′-sulfonyldianiline (DDS), *N*-allyl-4,4′-sulfonyldianiline,[13] or *N*-propyl-4,4′-sulfonyl-



VII

dianiline[13] and the requisite aldehyde. The yields ranged from 50 to 87%. 1,1′-[Sulfonylbis(*p*-phenyleneni-trilomethylene)]di-2-naphthol (VIII)[14] was ob-



VIII

tained in 80% yield by heating 2 equiv of 2-hydroxy-1-naphthaldehyde with 1 equiv of 4,4′-sulfonyldianiline in boiling *i*-AmOH for 30 sec.

Several formamidine derivatives of DDS and MADDS have been reported previously, including 4′-{*N*-[(dimethylamino)methylene]sulfanilyl}acetanilide[15] (IXa) and *N*′,*N*‴-(sulfonyldi-*p*-phenylene)bis(*N*,*N*-dimethylformamidine)[16,17] (IXb). Since amidine derivatives of this type can undergo hydrolytic scission yielding the corresponding amines, it was of interest to reinvestigate such compounds as potential repository drugs. The reaction of 4′-sulfanilylacetanilide[3] with

(11) P. E. Thompson, *Intern. J. Leprosy*, **35**, 605 (1967).

(12) P. E. Thompson, V. Bayles, and J. A. Waitz, manuscript in preparation.

(13) B. R. Baker, M. V. Querry, and A. F. Kadish, *J. Org. Chem.*, **15**, 402 (1950).

(14) P. P. T. Sah, J. F. Oneto, E. Rohrmann, and E. C. Kleiderer, *Rec. Trav. Chim.*, **68**, 141 (1949).

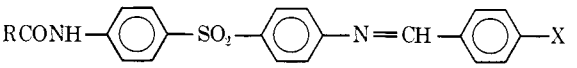
(15) N. Steiger, U. S. Patents 3,073,851 (1963), 3,133,078 (1964), and 3,153,033 (1964).

(16) G. R. Pettit and L. R. Carson, *Can. J. Chem.*, **43**, 2640 (1965).

(17) N. Steiger, U. S. Patents 3,135,755 (1964), 3,182,053 (1965), and 3,184,482 (1965).

TABLE I

4′-[N-(BENZYLIDENE)SULFANILYL]ANILIDES

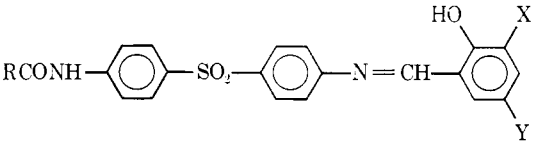


No.	R	X	Mp, °C	Yield purifd, %	Purifcn solvent	Reaction conditions Time, hr	Solvent	Formula	Analyses[a]
1	H	H	229–232	58	*i*-PrOH	6	*i*-PrOH	$C_{20}H_{16}N_2O_3S$	C, H, N, S
2	CH_3	Cl	226–228	25	*i*-PrOH	3	*i*-AmOH	$C_{21}H_{17}ClN_2O_3S$	C, H, N, Cl
3	CH_3	H	240–242	82	*a*	4	EtOH	$C_{21}H_{18}N_2O_3S$	C, H, N
4	CH_3	CO_2H	285 dec	26	MeCN	3	*i*-AmOH	$C_{22}H_{18}N_2O_5S \cdot 0.5H_2O$	C, H, N, H_2O
5	CH_3	$NHCOCH_3$	233–237	60	Me_2CO–Et_2O	2	*i*-AmOH	$C_{23}H_{21}N_3O_4S$	C, H, N
6	$(CH_2)_{10}CH_3$	Cl	145–149	21	*i*-PrOH	4	EtOH	$C_{31}H_{37}ClN_2O_3S$	C, H, N, Cl
7	$(CH_2)_{10}CH_3$	H	190–192	26	EtOH	4	EtOH	$C_{31}H_{38}N_2O_3S$	H, N; C[b]

[a] The product crystallized from the cooled reaction mixture and was collected and washed with Et_2O. [b] C: calcd, 71.78; found, 71.29.

TABLE II

4′-[N-(SALICYLIDENE)SULFANILYL]ANILIDES[a]

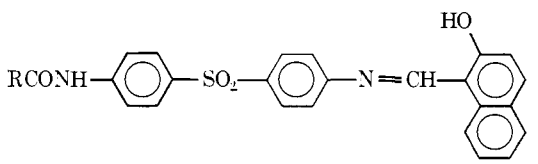


No.	R	X	Y	Mp, °C	Yield purifd %	Purifcn solvent	Reaction conditions Time, hr	Solvent	Formula
8	H	Br	Br	235–237	91	EtOH	0.5	EtOH	$C_{20}H_{14}Br_2N_2O_4S$
9	H	Cl	Cl	214–218	84	*b*	4	EtOH	$C_{20}H_{14}Cl_2N_2O_4S$
10	CH_3	Br	Br	274–276	90	*b*	3	*i*-AmOH	$C_{21}H_{16}Br_2N_2O_4S$
11	CH_3	Cl	Cl	259–260	97	*b*	3	*i*-AmOH	$C_{21}H_{16}Cl_2N_2O_4S$
12	CH_3	H	Cl	251–254	84	*b*	2	*i*-AmOH	$C_{21}H_{17}ClN_2O_4S$
13	CH_3	H	H	254–255[c]	91	*b*	3	*i*-AmOH	$C_{21}H_{18}N_2O_4S$
14	$(CH_2)_5CH_3$	H	H	171–174	67	MeCN	1	*i*-AmOH	$C_{26}H_{28}N_2O_4S$
15	$(CH_2)_{10}CH_3$	H	H	187–188	77	EtOH	4	EtOH	$C_{31}H_{38}N_2O_4S$

[a] All compounds analyzed for C, H, N. [b] The product crystallized from the cooled reaction mixture. [c] U. P. Basu and K. R. Chandran, *J. Indian Chem. Soc.*, **27**, 62 (1950), reported mp 243–244°.

TABLE III

4′-{N-[(2-HYDROXY-1-NAPHTHYL)METHYLENE]SULFANILYL}ANILIDES[a]

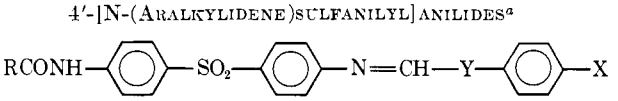


No.	R	Mp, °C	Yield purifd, %	Purifcn solvent	Reaction conditions Time, hr	Solvent	Formula
16	CH_3	281–283	95	*b*	0.5	*i*-AmOH	$C_{25}H_{20}N_2O_4S$
17	$(CH_2)_5CH_3$	215–216	69	MeCN	1	*i*-AmOH	$C_{30}H_{30}N_2O_4S$
18	$(CH_2)_{10}CH_3$	142–145	51	EtOH	3	EtOH	$C_{35}H_{40}N_2O_4S$

[a] All compounds analyzed for C, H, N. [b] The product crystallized from the cooled reaction mixture.

TABLE IV

4′-[N-(ARALKYLIDENE)SULFANILYL]ANILIDES[a]

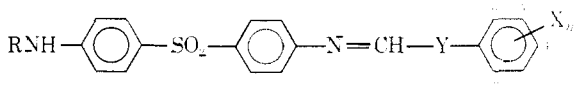


No.	R	Y	X	Mp, °C	Yield purifd, %	Purifcn solvent	Reaction conditions Time, hr	Solvent	Formula
19	CH_3	CH_2	H	245–255	5	*i*-PrOH	3	*i*-AmOH	$C_{22}H_{20}N_2O_3S \cdot 0.25H_2O$
20	CH_3	CH=CH	H	244–245[b]	51	MeOH	3	*i*-AmOH	$C_{23}H_{20}N_2O_3S$
21	CH_3	CH=CH	$N(CH_3)_2$	273–278	27	MeCN	1.5	*i*-PrOH	$C_{25}H_{25}N_3O_3S \cdot 0.25H_2O$
22	$(CH_2)_5CH_3$	CH=CH	$N(CH_3)_2$	219–220	26	MeCN	2	*i*-AmOH	$C_{30}H_{35}N_3O_3S$

[a] All compounds analyzed for C, H, N. [b] Lit. (footnote *c*, Table II) mp 219–220°.

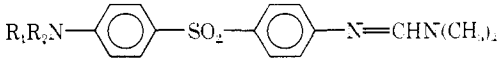
TABLE V

N-(ARALKYLIDENE- AND -BENZYLIDENE)-4,4′-SULFONYLDIANILINE DERIVATIVES[a]



No.	R	Y	X_n	Mp, °C	Yield purified, %	Purifien solvent	Reaction conditions— Time, hr	Solvent	Formula
23	H		H	211–212[b]	87	[c]	4	EtOH	$C_{19}H_{16}N_2O_2S$
24	H		4-$N(CH_3)_2$	235–237[d]	79	[c]	3	*i*-PrOH	$C_{21}H_{21}N_3O_2S$
25	$CH_2CH{=}CH_2$		2-OH-3,5-Cl_2	186–188	84	[c]	4	EtOH	$C_{22}H_{18}Cl_2N_2O_3S$
26	$CH_2CH_2CH_3$		2-OH-3,5-Cl_2	185–187	59	MeCN	1	EtOH	$C_{22}H_{20}Cl_2N_2O_3$
27	$CH_2CH_2CH_3$		H	210–212	50	MeCN	1	EtOH	$C_{22}H_{22}N_2O_2S$
28	H	CH=CH	4-$N(CH_3)_2$	244–246	62	*i*-PrOH	2	*i*-PrOH	$C_{23}H_{23}N_3O_2S$
29	H		4-$O(CH_2)_2N(C_2H_5)_2$	168–171	73	[c]	2	*i*-PrOH	$C_{25}H_{29}N_3O_3S$

[a] All compounds analyzed for C, H, N. [b] G. A. H. Buttle, T. Dewing, G. E. Foster, W. H. Gray, S. Smith, and D. Stephenson, *Biochem. J.*, **32**, 1101 (1938), reported mp 232°. [c] The product crystallized from the reaction mixture upon cooling and was collected, washed with fresh solvent, and dried. [d] Lit.[b] mp 252°.



IXa, $NR_1R_2 = NHCOCH_3$
b, $NR_1R_2 = N{=}CHN(CH_3)_2$
c, $NR_1R_2 = N(CHO)(CH_2)_2CH_3$
d, $NR_1R_2 = NH(CH_2)_2CH_3$
e, $NR_1R_2 = NHCO(CH_2)_{10}CH_3$

$POCl_3$ and DMF in C_6H_6 afforded two products that were separated, purified, and characterized. The first compound isolated melted at approximately 110°, resolidified, then melted at 195°. The ir spectrum showed peaks at 1700 (amide) and 1640 cm^{-1} (amidine), the nmr spectrum (DMSO-d_6) exhibited signals at 2.1 (CH_3CO) and 3.0 ppm [$(CH_3)_2N$], and the compound analyzed (C, H, N, S) for $C_{17}H_{19}N_3O_3S$. These results are in accord with structure IXa and suggest that the product (mp 260–262°) obtained previously from the condensation of 4′-sulfanilylacetanilide, benzenesulfonyl chloride, and DMF was not 4′-{N-[(dimethylamino)methylene]sulfanilyl}acetanilide as reported.[15] The second compound isolated melted at 142–144° and analyzed (C, H, N) correctly for $C_{18}H_{22}N_4O_2S$. The ir spectrum showed a strong peak at 1640 and no absorption at 1700 cm^{-1}. The nmr curve ($CDCl_3$) showed a signal at 3.0 ppm but no signal at 2.1 ppm. Further, the melting point was not depressed on admixture with a sample of N′,N‴-(sulfonyldi-*p*-phenylene)bis(N,N-dimethylformamidine) prepared from DDS (lit. mp 149–150°,[16] 131–133°[17]). Therefore, structure IXb was assigned to the second product.

Treatment of N-propyl-4,4′-sulfonyldianiline[13] with $POCl_3$ and DMF in C_6H_6 afforded 4′-{N-[(dimethylamino)methylene]sulfanilyl}-N-propylformanilide (IXc) in 70% yield. Hydrolysis of IXc with concentrated HCl in MeOH at room temperature gave N,N-dimethyl-N′-[*p*-(N-propylsulfanilyl)phenyl]formamidine monohydrochloride (IXd) (40%). 4′-{N-[(Dimethylamino)methylene]sulfanilyl}lauranilide (IXe) was prepared (29%) from 4′-sulfanilyllauranilide[3] utilizing the general procedure described for IXa and c.

The 4′-[N-(aralkylidene-, -benzylidene-, and -naphthylidene)sulfanilyl]anilides, 4′-{N-[(dimethylamino)-methylene]sulfanilyl}anilides, and related substances described in the present communication were supplied to Dr. P. E. Thompson and coworkers of these laboratories for evaluation as potential repository antimalarial agents against *Plasmodium berghei* in the mouse. As in previous work,[1-5,7] drugs were suspended in 5 ml/kg of benzyl benzoate–castor oil (BBCO, 40:60) and given to groups of 15–25 albino mice in a single 400-mg/kg sc dose. Subgroups of treated mice were subsequently challenged with *P. berghei* trophozoites at weekly or biweekly intervals. Assessment of repository action was based on the period of protection against patent infections afforded by a single dose of the drug. Activity is expressed as the number of weeks 50% of the mice were protected.

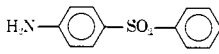
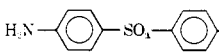
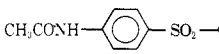
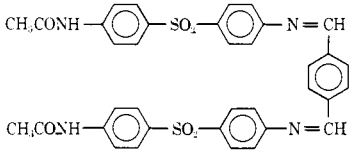
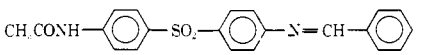
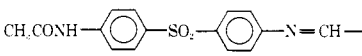
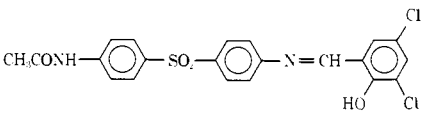
Among the 4′-[N-(benzylidene)sulfanilyl]anilides (III) (**1–7**, Table I), 4′-[N-(salicylidene)sulfanilyl]-anilides (IV) (**8–15**, Table II), 4′-{N-[(2-hydroxy-1-naphthyl)methylene]sulfanilyl}anilides (V) (**16–18**, Table III), and 4′-[N-(aralkylidene)sulfanilyl]anilides (VI) (**19–22**, Table IV), four compounds (**3**, **5**, **10**, **11**) exhibited noteworthy repository action. 4′-[N-(*p*-Acetamidobenzylidene)sulfanilyl]acetanilide (**5**), 4′-[N-(3,5-dibromosalicylidene)sulfanilyl]acetanilide (**10**), and 4′-[N-(3,5-dichlorosalicylidene)sulfanilyl]acetanilide (11) were very long acting and protected 50% of the mice for approximately 9 weeks against challenge with *P. berghei*. 4′-[N-(Benzylidene)sulfanilyl]acetanilide (**3**) protected mice for 6 weeks. Two of the N-(aralkylidene- and -benzylidene)-4,4′-sulfonyldianiline derivatives (VII) (**23–29**, Table V), namely, α-{[*p*-(N-allylsulfanilyl)phenyl]imino}-4,6-dichloro-*o*-cresol (**25**) and 4,6-dichloro-α-{[*p*-(N-propylsulfanilyl)phenyl]-imino}-*o*-cresol (**26**), also showed moderate repository activity and protected mice for periods of approximately 5 weeks. The other DDS derivatives (**23**, **24**, **27–29**, Table V), 1,1′-[sulfonylbis(*p*-phenylenenitrilomethylene)]di-2-naphthol (VIII), and the 4′-{N-[(dimethylamino)methylene]sulfanilyl}anilide and aniline derivatives (IXa–e) lacked appreciable repository action.

In view of the over-all potential of **3**, **5**, and 11 as repository antimalarial and antileprotic agents, these drugs were supplied to Dr. Charles C. Shepard, Communicable Disease Center, Atlanta, Ga., for evaluation against *Mycobacterium leprae* in mice. Each compound was completely suppressive when administered subcutaneously in single 200–400-mg/kg doses in BBCO at 2-month intervals.

A summary of the comparative antimalarial, antileprotic, and metabolic data on DDS, MADDS, DA-

TABLE VI

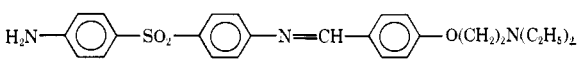
COMPARATIVE ANTIMALARIAL, ANTILEPROTIC, AND METABOLIC DATA ON DDS, MADDS, DADDS, PSBA, AND SELECTED 4′-[N-(BENZYLIDENE)SULFANILYL]ANILIDES[9,11]

Compound	Structure	Weeks mice protected		Rats[c]			
		P. berghei[a]	*M. leprae*[b]	Urinary excretion % excreted in 30 days	Urinary excretion Estd half-life, days	Peak blood level, μg/ml	Peak methemoglobin levels, g/100 ml
DDS		<1	2	57	9	13.8	3.9
MADDS		3.5		50	32	1.3	1.2
DADDS		12	>8	7	>200	0.2	0
PSBA		5–7	>8	40	55	0.4	0.2
3		6	>8	44	27		
5		9	>8	85	10		
11		9	>8	31	35	0.7	1.0

[a] Estimated number of weeks 50% of mice were protected following a single subcutaneous 400-mg/kg dose of drug suspended in benzyl benzoate–castor oil (40:60). [b] First drug injection was 400 mg/kg given 58 days after infection with *Mycobacterium leprae;* subsequent injections were 200 mg/kg at intervals of 0.5, 1, or 2 months. [c] Drugs given as a single subcutaneous dose of 400 mg/kg in a volume of 5 ml/kg of 1.5% pectin and 0.1% Tween 60 in distilled water.

DDS, PSBA, and selected 4′-[N-(benzylidene)sulfanilyl]anilides (**3**, **5**, 11) in mice and rats is presented in Table VI.[9,11] The duration of protection against challenge with *P. berghei* afforded by a single subcutaneous 400-mg/kg dose of **3**, **5**, and 11 ranged from 6 to 9 weeks and was intermediate between the short-acting DDS and the very long acting DADDS. By contrast, each sulfone protected mice against *M. leprae* infections for >8 weeks following a single 200–400-mg/kg dose, thus reflecting earlier observations that *M. leprae* is more sensitive to DDS than is *P. berghei.*[9] With the exception of 4′-[N-(*p*-acetamidobenzylidene)sulfanilyl]acetanilide (**5**), the pattern of urinary excretion in rats also was intermediate between DDS and DADDS. 4′-[N-(3,5-Dichlorosalicylidene)-sulfanilyl]acetanilide (11) produced much lower peak blood sulfone levels and methemoglobin levels than did DDS. These results suggest that **3**, **5**, and 11 might provide a relatively more intense, albeit less prolonged, chemotherapeutic effect than an equivalent dose of DADDS, and be much safer drugs than DDS.

Although N-{*p*-[2-(diethylamino)ethoxy]benzylidene}-4,4′-sulfonyldianiline (X) lacked appreciable



X

repository antimalarial activity and failed to protect mice from challenge with *P. berghei* for even 1 week, the compound exhibited strong therapeutic effects against *P. berghei* when administered to mice continuously in the diet for 6 days.[7] The SD_{90} (daily dose required for 90% suppression of the parasitemia) for X, DDS, DFDDS, and quinine was 0.4, 0.5, <0.3, and 74.5 mg/kg, respectively. Therefore, N-{*p*-[2-(diethylamino)ethoxy]benzylidene}-4,4′-sulfonyldianiline had an order of activity similar to DDS and DFDDS against the sensitive parent line and was approximately 190 times as potent as quinine. However, in view of the inherent cross-resistance liability between X and DDS, the compound was not studied further.

Experimental Section[18,19]

4′-[N-(Benzylidene)sulfanilyl]anilides (III), 4′-[N-(salicylidene)sulfanilyl]anilides (IV), 4′-{N-[(2-hydroxy-1-naphthyl)-methylene]sulfanilyl}anilides (V), 4′-[N-(aralkylidene)sulfanilyl]anilides (VI), and N-(aralkylidene- and -benzylidene)-4,4′-sulfonyldianiline Derivatives (VII) (1–29, Tables I–V). General Method.—A mixture of the appropriately substituted sulfone (chosen from among 4,4′-sulfonyldianiline, 4′-sulfanilylformanilide,[3] 4′-sulfanilylacetanilide,[3] 4′-sulfanilylheptananilide,[3] 4′-sulfanilyllauranilide,[3] N-allyl-4,4′-sulfonyldianiline,[13] and N-propyl-4,4′-sulfonyldianiline[13]) and 2 equiv of the desired aldehyde was heated under reflux for 0.5–4 hr in the solvent indicated. When crystallization occurred on cooling, the product was collected by filtration and washed with fresh solvent or recrystallized. When crystallization did not occur, the solution was concentrated on a rotary evaporator, and the residue was crystallized from the solvent specified in the tables.

1,1′-[Sulfonylbis(*p*-phenylenenitrilomethylene)]di-2-naphthol (VIII).—A hot solution of 17.2 g (0.10 mole) of 2-hydroxy-1-naphthaldehyde in 150 ml of *i*-AmOH was added to a solution of

(18) Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus.

(19) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Water determinations were by the Karl Fischer method.

12.4 g (0.050 mole) of 4,4′-sulfonyldianiline in 400 ml of boiling *i*-AmOH. After 30 sec, crystallization of an orange solid began, and the entire mixture rapidly solidified. The mixture was filtered hot, and the insoluble material was collected and washed with *i*-AmOH and Et_2O. The product was dried *in vacuo* at 65° for 24 hr to give 22.3 g (80%), mp 284–287° (lit.[14] mp 235°). *Anal.* ($C_{34}H_{24}N_2O_4S$) C, H, N.

4′-{N-[(Dimethylamino)methylene]sulfanilyl}acetanilide (IXa) and N′,N‴-(Sulfonyldi-*p*-phenylene)bis(N,N-dimethylformamidine) (IXb).—A solution of 7.7 g (0.05 mole) of $POCl_3$ in 25 ml of C_6H_6 was added dropwise over 20 min to a solution of 7.3 g (0.1 mole) of DMF in 25 ml of C_6H_6. The maximum temperature was 35°. After stirring for 20 min at room temperature, a solution of 14.5 g (0.05 mole) of 4′-sulfanilylacetanilide[3] in 75 ml of DMF was added. The resulting solution was heated at 60–70° for 6 hr and, after cooling to room temperature, the mixture was triturated with three 200-ml portions of Et_2O. The residue was treated with excess 1 *N* NaOH and extraction was attempted with C_6H_6. The aqueous layer, which still contained considerable amounts of insoluble material, was then further extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with dilute NaOH, dried (Na_2SO_4), and concentrated to an oil which slowly crystallized to yield 13.1 g of crude product, mp 155–160°. This was washed with hot C_6H_6 and recrystallized twice from $CHCl_3$–Et_2O to obtain 4.3 g (25%) of material which melted at *ca.* 110°, resolidified, then melted at 195° (lit.[15] mp 260–262°). The ir curve (KBr) showed peaks at 1700 (amide) and 1640 cm^{-1} (amidine); the nmr curve (DMSO-d_6) had signals at 2.1 (CH_3CO) and 3.0 ppm [$(CH_3)_2N$]. *Anal.* ($C_{27}H_{29}N_5O_3S$) C, H, N, S.

Upon concentration of the C_6H_6 extract of the NaOH mixture followed by two recrystallizations of the residue from *i*-PrOH, there was obtained 1.9 g of a tan solid, mp 142–144°, which was not depressed on admixture with a sample of N′,N‴-(sulfonyldi-*p*-phenylene)bis(N,N-dimethylformamidine) (mp 143–145°) prepared from 4,4′-sulfonyldianiline;[16,17] ir curve (KBr), 1640 cm^{-1} with no absorption at 1700 cm^{-1}; nmr curve ($CDCl_3$), 3.0 ppm with no signal at 2.1 ppm. *Anal.* ($C_{18}H_{22}N_4O_2S$) C, H, N, S.

4′-{N-[(Dimethylamino)methylene]sulfanilyl}-N-propylformanilide (IXc).—$POCl_3$ (5.35 g, 0.035 mole) was added dropwise to a solution of 5.1 g (0.070 mole) of DMF in 75 ml of C_6H_6. After stirring for 1.5 hr at room temperature, a solution of N-propyl-4,4′-sulfonyldianiline[18] in 70 ml of DMF and 200 ml of C_6H_6 was added. The temperature rose spontaneously from 24 to 34°, and was then raised to 65–75° for 4 hr. The mixture was concentrated on a rotary evaporator and the residue was treated with excess dilute NaOH. The mixture was extracted with $CHCl_3$, and the extracts were dried (K_2CO_3) and concentrated to an oil which crystallized from *i*-PrOH. Two recrystallizations from *i*-PrOH gave 9.2 g (70%); mp 148–150°; ir ($CHCl_3$), 1680, 1640 cm^{-1}. *Anal.* ($C_{19}H_{23}N_3O_3S$) C, H, N.

N,N-Dimethyl-N′-[*p*-(N-propylsulfanilyl)phenyl]formamidine Monohydrochloride (IXd).—A solution of 3.1 g (0.0083 mole) of IXc in 200 ml of MeOH and 5 ml of concentrated HCl was allowed to stand at 25° for 48 hr. The solution was concentrated to an oil which crystallized on treatment with *i*-PrOH–Et_2O. This was combined with 0.7 g of similar material obtained from a previous reaction and recrystallized twice from MeCN to obtain 1.7 g (40%), mp 212° dec. The ir curve had a split peak at 1720 and 1705 cm^{-1}.[16] A sample of the base, prepared by dissolving 50 mg of the hydrochloride in H_2O, adding excess NaOH, extracting with $CHCl_3$, drying (K_2CO_3), and concentrating, gave a peak at 1635 cm^{-1}. *Anal.* ($C_{18}H_{23}N_3O_2S \cdot HCl$) C, H, N.

4′-{N-[(Dimethylamino)methylene]sulfanilyl}lauranilide (IXe).—A solution of 1.53 g (0.010 mole) of $POCl_3$ in 25 ml of C_6H_6 was added dropwise to a solution of 1.46 g (0.020 mole) of DMF in 25 ml of C_6H_6. A slurry of 4.31 g (0.010 mole) of 4′-sulfanilyllauranilide[3] in 150 ml of C_6H_6 was then added, and the mixture was heated at 65–70° for 5 hr. After cooling to room temperature, the precipitate was collected and washed with ether. Treatment with excess dilute NaOH, extraction with C_6H_6, and concentration of the extracts to dryness gave a solid which after two recrystallizations from EtOH gave 1.40 g (29%); mp 125–127°; ir (KBr) 1710, 1650 cm^{-1}. *Anal.* ($C_{32}H_{55}N_3O_3S$) C, H, N.

Acknowledgments.—The authors wish to express their appreciation to Dr. Paul E. Thompson and coworkers of these laboratories for the antimalarial evaluation of these compounds, and to Dr. Charles C. Shepard of the Communicable Disease Center, Atlanta, Ga., for the leprosy studies. We also thank Dr. J. M. Vandenbelt and coworkers for the spectral determinations, and Mr. Charles E. Childs and associates for the microanalyses.