collected by filtration and crystallized three times from MeCN to give 5.3 g (68%) of a bright yellow solid, mp 238–241° dec.

4'[(2-Acetamido-5-thiazolyl)sulfonyl]acetanilide (X).—A mixture of 29.7 g (0.10 mole) of N-(5-sulfanilyl-2-thiazolyl)acetamide,[32] 75 ml of HOAc, and 13 g (0.13 mole) of Ac_2O was heated to boiling when a thick slurry formed. DMF (50 ml) was added and the mixture was heated under reflux for 1.5 hr. After cooling, the precipitate was collected by filtration and washed (H_2O). Recrystallization from DMF–EtOH gave 28.5 g (84%), mp 313–314° dec. *Anal.* ($C_{13}H_{13}N_3O_4S_2$) C, H, N.

3',3'''-Sulfonylbisacetanilide (XI).—To a solution of 9.3 g (0.038 mole) of 3,3'-sulfonyldianiline[33] in 100 ml of Me_2CO and 7.5 ml of pyridine was added dropwise 8.8 g (0.11 mole) of AcCl, keeping the temperature below 40° by adjusting the rate of addition. After standing 24 hr at room temperature, the mixture was poured into 5% HCl, and the resulting precipitate collected. Recrystallization from EtOH gave 6.4 g (51%), mp 215–218°. *Anal.* ($C_{16}H_{16}N_2O_4S$) C, H, N.

3,3'-[Sulfonylbis(*p*-phenyleneiminomethylene)]di-2-thiazolidinethione (XII).—A mixture of 24.8 g (0.10 mole) of DDS, 23.8 g (0.20 mole) of 2-thiazoline-2-thiol, and 18 ml (0.20 mole) of formalin in 500 ml of *i*-PrOH was stirred and heated under reflux for 24 hr. The product was collected by filtration of the hot reaction mixture and recrystallized from DMF–H_2O to give 18 g (35%), mp 225–226°. *Anal.* ($C_{20}H_{22}N_4O_2S_5$) C, H, N, S.

(32) L. L. Bambas, *J. Am. Chem. Soc.*, **67**, 671 (1945).
(33) Tennessee Corp., Atlanta, Ga.

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. David B. Capps and Dr. Leslie M. Werbel for the preparation of several of the compounds described herein, Mr. William Pearlman for the performance of the hydrogenations described, Dr. J. M. Vandenbelt and coworkers for the spectral and solubility determinations, and Mr. Charles E. Childs and associates for the microanalyses.

Repository Drugs. V. 4',4'''-[*p*-Phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (PSBA) and Related 4',4'''-[Bis(imino-*p*-phenylenesulfonyl)]bisanilides, a Novel Class of Long-Acting Antimalarial and Antileprotic Agents[1]

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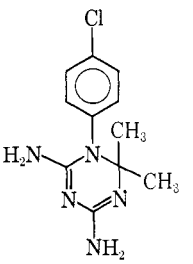
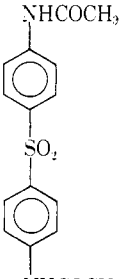
Received January 6, 1969

Various 4',4'''-[bis(imino-*p*-phenylenesulfonyl)]bisanilides (III–VI, VIII) 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 phthalaldehyde or naphthalenedicarboxaldehyde with the requisite 4'-sulfanilylanilide. Among them, 4',4'''-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (PSBA) (IX) fulfilled the above requirements and showed remarkable repository effects alone against *Mycobacterium leprae* and alone or in combination with cycloguanil pamoate against *Plasmodium berghei* in mice and *Plasmodium cynomolgi* in monkeys. Structure–activity relationships are discussed.

A systematic search for various types of repository drugs in these laboratories led successively to the development of cycloguanil pamoate (I),[2–4] a long-acting antimalarial and antileishmania drug; acedapsone (DADDS) (II),[1,5–8] a repository antileprotic and antimalarial agent; and cycloguanil pamoate–acedapsone (DADDS),[1,5,6] a combination antimalarial drug with protracted action against drug-resistant strains.[9]



I



II

Among the 4'-sulfanilylanilide congeners of 4,4'-sulfonyldianiline (DDS) investigated previously,[1,5] 4',4'''-sulfonylbisacetanilide (acedapsone, DADDS) (II) conferred the longest protection and has been studied extensively both in experimental animals and in man.[5–12]

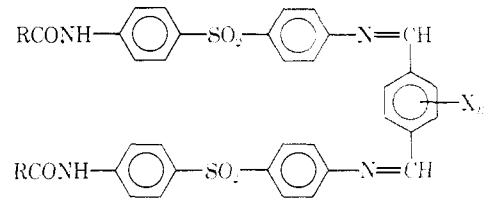
(1) Previous paper: E. F. Elslager, Z. B. Gavrilis, A. A. Phillips, and D. F. Worth, *J. Med. Chem.*, **12**, 357 (1969).
(2) E. F. Elslager and P. E. Thompson, Abstracts, 9th National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minn., June 1964, p 6A.
(3) P. E. Thompson, B. J. Olszewski, E. F. Elslager, and D. F. Worth, *Am. J. Trop. Med. Hyg.*, **12**, 481 (1963).
(4) Camolar®.
(5) E. F. Elslager and D. F. Worth, *Nature*, **206**, 630 (1965).
(6) P. E. Thompson, B. Olszewski, and J. A. Waitz, *Am. J. Trop. Med. Hyg.*, **14**, 343 (1965).
(7) (a) C. C. Shepard, *Proc. Soc. Exp. Biol Med.*, **124**, 430 (1967); (b) C. C. Shepard, D. H. McRae, and J. A. Habas, *ibid.*, **122**, 893 (1966).
(8) Acedapsone is the nonproprietary name for 4',4'''-sulfonylbisacetanilide. In the biological literature acedapsone has also been referred to as sulfadiamine, 4,4'-diacetyldiaminodiphenyl sulfone, 4,4'-diacetylaminodiphenyl sulfone, N,N'-diacetyl-4,4'-diaminodiphenyl sulfone, and DADDS. Hansolar® is a proprietary name for acedapsone. The proprietary name for the acedapsone–cycloguanil pamoate combination is Dapolar®.
(9) For recent reviews, see (a) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966, p 136; (b) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1966," C. K. Cain, Ed., Academic Press, New York, N. Y., 1967, p 131.
(10) D. F. Clyde, Abstracts, Eighth International Congresses on Tropical Medicine and Malaria, Teheran, Iran, Sept 7–15, 1968, p 1380.
(11) (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).
(12) C. C. Shepard, J. G. Tolentino, and D. H. McRae, *ibid.*, **17**, 192 (1968).

Against *Plasmodium berghei* infections in mice, a single 100–400-mg/kg sc dose of DADDS almost invariably prevented or strongly suppressed patent infections through 6–14 weeks. A single 50-mg/kg im dose of DADDS prevented patent *Plasmodium cynomolgi* infections in monkeys for 63–268 (average 158) days and greatly suppressed the parasitemia for many weeks longer. A comparison of DADDS, cycloguanil pamoate (I),[4] and a 1:1 cycloguanil pamoate–DADDS mixture against lines of *P. berghei* highly resistant to either DDS or cycloguanil hydrochloride demonstrated that the mixture had broader repository action against the drug-resistant lines than either drug alone.[6] In studies against experimental leprosy infections in the mouse, a single 6-mg/kg sc dose of DADDS administered at 2-month intervals afforded nearly complete suppression of *Mycobacterium leprae*, while larger doses were completely suppressive.[7a]

The antimalarial properties of the cycloguanil pamoate–DADDS mixture have been evaluated in approximately 1000 human subjects.[10,11] Against *Plasmodium vivax*, the minimum period of protection afforded by a single, intramuscular dose containing 3.2–10 mg/kg of each component ranged from 5 months in strains susceptible to chlorguanide to no protection in strains highly resistant to chlorguanide. Against *Plasmodium falciparum*, the following minimum protection periods were obtained: (1) strains susceptible to chlorguanide and pyrimethamine, 4 months; (2) strains resistant to chlorguanide and pyrimethamine, 3 months; and (3) strains from southeast Asia resistant to chlorguanide, pyrimethamine, and the 4-aminoquinolines, variable, approximately 2 months. The results of a preliminary clinical trial with DADDS alone in lepromatous leprosy have also been promising.[12] In this study, a single 225-mg im dose of DADDS administered every 77 days was as effective as oral DDS given in a dosage of 100 mg daily over a treatment period of 48 weeks.[12]

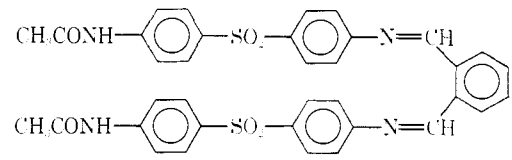
Inasmuch as DADDS is apparently dependent upon deacetylation for activity and affords only extremely low sulfone blood levels, a repository sulfone that is less dependent on enzymatic deacylation for activity and enables higher blood sulfone levels than DADDS might fulfill a useful need. Therefore, attention was focused on the design and synthesis of novel sulfone molecules that might undergo slow, nonenzymatic hydrolytic scission directly upon contact with body tissues and fluids. This report describes the synthesis and properties of various 4′,4‴-[bis(imino-*p*-phenylenesulfonyl)]bisanilides, several of which fulfill the above requirements.

The condensation of 1 equiv of terephthalaldehyde, 2,3,5,6-tetrachloroterephthalaldehyde,[13] or 2,3,5,6-tetramethylterephthalaldehyde[14] with 2 equiv of 4′-sulfanilylformanilide (MFDDS),[1] 4′-sulfanilylacetanilide (MADDS),[1] 4′-sulfanilylpropionanilide,[1] 4′-sulfanilylheptananilide,[1] or 4′-sulfanilyllauranilide[1] in EtOH, AcOH, or *i*-AmOH afforded the corresponding 4′,4‴-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]-bisanilides (III) (**1–7**, Table I) (procedures I–III) in

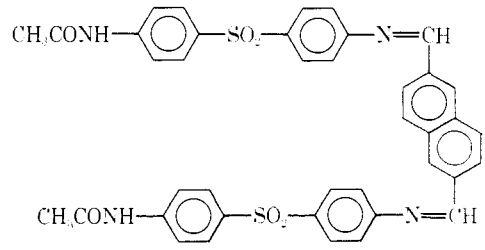


III

3–81% yield. Similarly, 4′,4‴-[*o*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (IV) (**9**, Table II) and 4′,4‴-[2,6-naphthylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (V) (**10**, Table II) were prepared from 4′-sulfanilylacetanilide (MADDS),[1] phthalaldehyde, and 2,6-naphthalenedi-

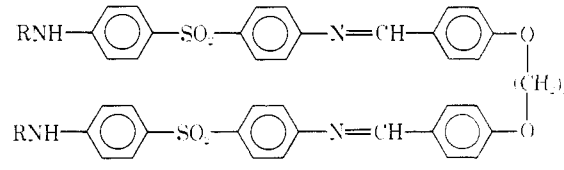


IV



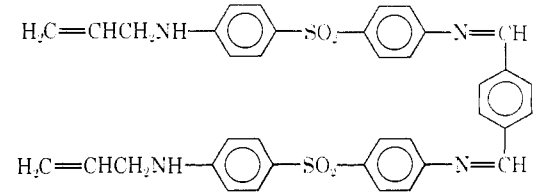
V

carboxaldehyde[15] in 19 and 43% yield, respectively. The condensation of 4,4′-(ethylenedioxy)benzaldehyde[16] with 2 equiv of 4,4′-sulfonyldianiline (DDS) or 4′-sulfanilylacetanilide (MADDS)[1] (procedure V) gave N,N′-[ethylenebis(oxy-*p*-phenylenemethylidyne)]bis(4-sulfanilylaniline) (VIa) (**11**, Table II) (96%) and 4′,4‴-



VIa, R = H
b, R = $COCH_3$

[ethylenebis(oxy-*p*-phenylenemethylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (VIb) (**12**, Table II) (54%). N,N′-(*p*-Phenylenedimethylidyne)bis[4-N-allylsulfanilyl)aniline] (VII) was obtained in 67% yield by



VII

(13) 2,3,5,6-Tetrachloroterephthalaldehyde was generously supplied by Mr. Charles E. Granito, Diamond Shamrock Corp., Painesville, Ohio 44077.

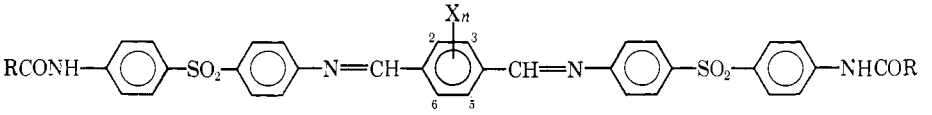
(14) 2,3,5,6-Tetramethylterephthalaldehyde was generously supplied by Dr. B. H. Klanderman, Research Laboratories, Eastman Kodak Co., Rochester, N. Y. 14650; see B. H. Klanderman, *J. Org. Chem.*, **31**, 2618 (1966).

(15) 2,6-Naphthalenedicarboxaldehyde was generously supplied by Dr. P. W. Storms, Marathon Oil Co., Denver Research Center, Littleton, Colo.; see P. W. Storms and P. R. Taussig, *J. Chem. Eng. Data*, **11**, 272 (1966).

(16) W. J. P. Neish, *Rec. Trav. Chim.*, **66**, 435 (1947).

TABLE I

4′,4‴-[*p*-PHENYLENEBIS(METHYLIDYNEIMINO-*p*-PHENYLENESULFONYL)]BISANILIDES[a]

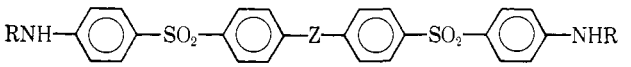


No.	R	X_n	Mp, °C	Yield purifd, %	Procedure	Purifcn solvent[b]	Formula	Analyses[23]
1	H	H	>300	81	I	A	$C_{34}H_{26}N_4O_6S_2$	C, H, N
2	CH_3	2,3,5,6-Cl_4	290	72	II	B	$C_{36}H_{26}Cl_4N_4O_6S_2 \cdot H_2O$	C, H, N, H_2O
3	CH_3	H	>300	76	I	A	$C_{36}H_{30}N_4O_6S_2 \cdot 1.5H_2O$	C, H, N, H_2O
4	C_2H_5	H	>300	26	I	C	$C_{38}H_{34}N_4O_6S_2$	C, H, N
5	CH_3	2,3,5,6-$(CH_3)_4$	280	67	II	D	$C_{46}H_{38}N_4O_6S_2 \cdot 0.4H_2O$	C, H, N, H_2O
6	$(CH_2)_5CH_3$	H	272–275	3	III	E	$C_{46}H_{50}N_4O_6S_2 \cdot 0.67H_2O$	C, H, N
7	$(CH_2)_{10}CH_3$	H	265–268	50	I	F	$C_{56}H_{70}N_4O_6S_2$	C, H, N

[a] Compounds are yellow solids. [b] A, EtOH; B, AcOH; C, DMSO; D, *i*-PrOH; E, Et_2O; F, dioxane.

TABLE II

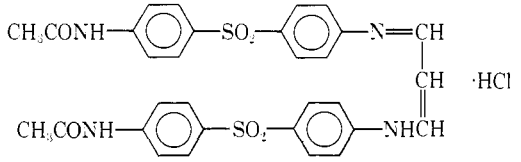
OTHER 4′,4‴-[BIS(IMINO-*p*-PHENYLENESULFONYL)]BISANILINES AND ANILIDES[a]



No.	R	Z	Mp, °C	Yield purifd, %	Pro-cedure	Purifcn solvent[b]	Formula	Analyses[23]
8	$COCH_3$	N=CHCH=CHNH	217–225 dec	46	IV	A	$C_{31}H_{28}N_4O_6S_2 \cdot HCl \cdot 2.25H_2O$	C, H, Cl, N, H_2O
9	$COCH_3$	N=CH-*o*-C_6H_4CH=N	235	19	V	B	$C_{36}H_{30}N_4O_6S_2 \cdot 0.5H_2O$	C, H; N[c]
10	$COCH_3$	N=CH-2,6-$C_{10}H_6$CH=N[d]	>300	43	I	C	$C_{40}H_{32}N_4O_6S_2 \cdot 0.5H_2O$	C, H, N
11	H	$(N=CH\text{-}p\text{-}C_6H_4O)_2(CH_2)_2$	272–275	96	V	B	$C_{40}H_{34}N_4O_6S_2$	C, H, N
12	$COCH_3$	$(N=CH\text{-}p\text{-}C_6H_4O)_2(CH_2)_2$	276–278	54	V	D	$C_{44}H_{38}N_4O_8S_2$	C, H, N

[a] Compounds range from yellow to red. [b] A, MeOH; B, *i*-PrOH; C, EtOH; D, DMF-*i*-PrOH. [c] N: calcd, 8.15; found, 7.50. [d] $C_{10}H_6$ represents naphthylene.

the reaction of N-allyl-4,4′-sulfonyldianiline[17] and terephthalaldehyde in EtOH. 4′,4‴-[1-Propen-1-yl-3-ylidenebis(imino-*p*-phenylenesulfonyl)]bisacetanilide monohydrochloride (VIII) (**8**, Table II), which contains an aliphatic side-chain interruption between the two

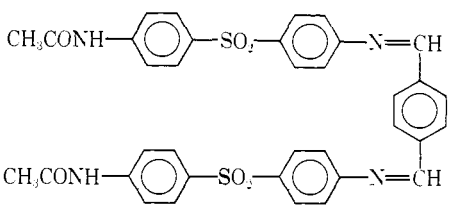


VIII

sulfone moieties, was prepared from 1 equiv of 1,1,3,3-tetraethoxypropane and 2 equiv of 4′-sulfanilylacetanilide (MADDS)[1] in MeOH and HCl in 46% yield (procedure IV).

The 4′,4‴-[bis(imino-*p*-phenylenesulfonyl)]bisanilides 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,[1-3,5,6] drugs were suspended in 5 ml/kg of benzyl benzoate–castor oil (40:60) (BBCO) 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.

Among the 4′,4‴-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisanilides (III) (**1**–**7**, Table I), two compounds exhibited noteworthy repository action. 4′,4‴-[*p*-Phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisformanilide (PSBF) (**1**) was very long acting and protected mice for >9 weeks against challenge with *P. berghei*. 4′,4‴-[*p*-Phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (PSBA) (IX) protected mice for 5–7 weeks, depending on particle size (fine to medium), a period intermediate between the short-acting DDS and the very long acting



IX

DADDS.[18] These results suggested that PSBA should provide higher blood levels than DADDS and still afford protection for reasonable periods of time. None of the bisanilides (**4**, **6**, **7**, Table I) derived from higher molecular weight acids exhibited promising repository activity. As a group, the 4′,4‴-[bis(imino-*p*-phenylenesulfonyl)]bisanilines and anilides summarized in Table II were also less promising than PSBA and PSBF, and compounds VI–VIII failed to protect all of the mice for even 1 week.

Expanded repository antimalarial studies with PSBA were carried out utilizing *P. berghei* in rats and *P. cyno-*

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

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

molgi in monkeys.[18,19] 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.[18] 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.[6,18] This presumptive evidence that the scission of PSBA is not enzyme dependent is corroborated by physical–chemical data (Experimental Section) which indicates that PSBA is 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.[19] The mean duration of protection after a single 50-mg/kg im dose of medium particle size PSBA ranged from 4.4 months in isopropyl myristate–peanut oil (25:75) (IMPO) to 5.1 months in BBCO.

In therapeutic tests in mice and rats, a single 400-mg/kg sc dose of PSBA produced strong suppression of the parasitemia within 48 hr and all animals had negative thick and thin smears on days 5–7 after dosing. A 50-mg/kg im dose of PSBA suppressed patent infections of *P. cynomolgi* in monkeys as rapidly as a substantial intramuscular dose of DDS.[19]

Tests against resistant lines of *P. berghei* in mice indicate that PSBA, like DADDS, is effective against strains resistant to cycloguanil but not against strains resistant to DDS. However, a 1:1 mixture of cycloguanil pamoate and PSBA was effective against both the cycloguanil- and DDS-resistant lines.[19]

In view of the over-all potential of PSBA as a repository antimalarial and antileprotic agent, the drug was supplied to Dr. Charles C. Shepard, Communicable Disease Center, Atlanta, Ga., for evaluation against *M. leprae* in mice. The drug was completely suppressive when administered subcutaneously in a single 400-mg/kg dose in BBCO at 2-month intervals.[7a] PSBA also exhibited modest repository antituberculosis activity against *Mycobacterium tuberculosis* $H_{37}Rv$ in mice when administered subcutaneously in a single 400–800-mg/kg dose in IMPO.[20]

A summary of comparative antimalarial, antileprotic, and metabolic data on DDS, MADDS, DADDS, PSBA, and PSBF in mice and rats is presented in Table III.[7,18]

The length of action of PSBA against *P. berghei* in mice was intermediate between the short-acting DDS and the very long acting DADDS. The duration of protection of DADDS and PSBA against *M. leprae* in mice was similar, thus reflecting earlier observations that *M. leprae* is more sensitive to DDS than *P. berghei*.[7b] The pattern of urinary excretion of PSBA was also intermediate between that of DDS and DADDS. PSBA produced much lower peak blood levels and methemoglobin levels than did DDS. These results suggest that PSBA might provide a relatively more intense, albeit less prolonged, chemotherapeutic effect than an equivalent dose of DADDS, and be a much safer drug than DDS.

Preclinical toxicological studies with the intermediately long acting PSBA were carried out in mice, rats, dogs, and monkeys.[21] The compound was supplied for test purposes in 4-ml sterilized vials as a suspension containing 175 mg of PSBA/ml in IMPO. The intraperitoneal LD_{50} of PSBA in rats (>3170 mg/kg) could not be determined realistically because (1) the size of the dose was limited by the volume which could be administered, and (2) all surviving animals sacrificed 21 days after dosing still contained large quantities of drug in their peritoneal cavities.[21] Up to 13 weekly intramuscular doses of 50 mg/kg in rats, 25 mg/kg in dogs, and 25 or 50 mg/kg in monkeys failed to produce consistent clinical, laboratory, or pathological changes, except as related to the sites of injection. Characteristically, a chronic granulomatous response developed in the muscle at the site of injection, with vigorous foreign body giant cell proliferation and final fibrosis of the site. Crystals of drug were still found at the injection sites after 12 weeks.[21] Suspensions of PSBA in IMPO injected intramuscularly in pregnant mice and rats, either during the organogenesis period or the perinatal–postnatal period, did not significantly alter the course or outcome of the pregnancy at dosage levels ranging from 10 to 75 mg/kg.[21] Single injections of PSBA in male rats and mice at doses of 75 mg/kg and in inseminated female rats and mice at doses of 10–75 mg/kg did not adversely affect the fertility or subsequent reproductive performance of the animals.[21]

The results of these antimalarial, antileprotic, and toxicological studies encourage further evaluation of PSBA alone, or in combination with cycloguanil pamoate, in connection with the prevention and eradication of malaria, and alone in the tretament and prophylaxis of leprosy.

Table III

Comparative Antimalarial, Antileprotic, and Metabolic Data on DDS, MADDS, DADDS, PSBA, and PSBF[7,a15]

				Rats[b]			
		Weeks mice protected		Urinary excretion			Peak methemoglobin levels, g/100 ml
Drug	Structure	*P. berghei*[a]	*M. leprae*	% excreted in 30 days	Estd half-life, days	Peak blood level, μg/ml	
DDS	p-$H_2NC_6H_4SO_2C_6H_4$-p-NH_2	<1	2	57	9	13.8	3.9
MADDS	p-$H_2NC_6H_4SO_2C_6H_4$-p-$NHCOCH_3$	3.5		50	32	1.3	1.2
DADDS	II[c]	12	>8	7	>200	0.2	0
PSBA	IX[c]	5–7	>8	40	55	0.4	0.2
PSBF	III, R = H, X_n = H[c]	>9					

[a] Estimated number of weeks 50% of mice were protected following a single 400-mg/kg sc dose of drug suspended in benzyl benzoate–castor oil (40:60). [b] 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. [c] See text for structure.

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

(20) For a description of the test method, see L. M. Werbel, E. F. Elslager, M. W. Fisher, Z. B. Gavrilis, and A. A. Phillips, *J. Med. Chem.*, **11**, 411 (1968).

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Experimental Section[22,23]

4′,4‴-[*p*-Phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisanilides (III) (Table I) and Other 4′,4‴-[Bis(imino-*p*-phenylenesulfonyl)]bisanilines and -anilides (IV–VI, VIII) (Table II). Procedure I. 4′,4‴-[*p*-Phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (PSBA) (IX).—A hot, filtered solution of 6.7 g (0.05 mole) of terephthalaldehyde (Aldrich) in 200 ml of EtOH was added to a hot, stirred solution of 29.0 g (0.10 mole) of 4′-sulfanilylacetanilide (MADDS)[1] in 2 l. of EtOH. The solution was heated at reflux for 3 hr, then concentrated to 1 l. over an additional 2.5-hr period, at which time the product began to precipitate. The mixture was kept at room temperature overnight and filtered to give 10.5 g of a first crop. Concentration of the filtrate gave two additional crops weighing 11.5 and 5.5 g, respectively. The crops were slurried in boiling EtOH, recovered by filtration, and dried at 75° *in vacuo;* total yield, 27.0 g (76%). All three fractions were pale yellow and melted above 300°. The uv absorption curves (DMF) showed maxima at 347 mμ (E_1^1 550) and 287 mμ (E_1^1 740) after correction for H_2O. A convenient uv assay method for determining the amount of MADDS in PSBA involves treatment of the Schiff base with 0.5 *N* HCl in MeOH. After solution was complete, an appropriate dilution in MeOH was made weakly alkaline with a minimum amount of KOH solution. The spectrum of the solution, which now contained MADDS and the tetramethyl acetal of terephthalaldehyde, was determined and compared to a standard spectrum of MADDS (E_1^1 920 at 294 mμ). Typical results were within ±3% of that expected. This procedure was generally applicable to the assay of the sulfone moiety of the other Schiff bases described herein.

In an effort to determine the solubility of PSBA in aqueous media, a 50-mg sample was agitated in 10 ml of a 0.1 *N* pH 7 phosphate buffer for 1 hr. After centrifugation a uv absorption curve was obtained from the clear supernatant solution. The absorption at 350 mμ showed a concentration of <0.001 mg of PSBA/ml; however, there were weak maxima at 289 (A = 0.61), 272 (A = 0.68), and 258 mμ (A = 0.73) from the hydrolysis products. An absorption curve obtained from the insoluble residue showed only intact PSBA.

Because of the difficulties inherent in obtaining consistent uv absorption curves in H_2O or even MeOH–H_2O mixtures due to lack of solubility and stability, mixtures of DMF and H_2O were chosen for the estimation of the hydrolysis rate, since this allowed for complete solution in partially aqueous systems. Solutions of PSBA (0.002%) were prepared and kept at room temperature in the solvents indicated (Table IV), and the half-life of PSBA was estimated from the periodic examination of the decrease in absorption at 350 mμ. Table IV shows the dramatic decrease in the stability of PSBA in solution with increasing concentrations of H_2O. Besides the decrease in the absorption at 350 mμ, these curves showed a peak emerging at 298 mμ which was consistent with the formation of MADDS and/or DDS. Visual examination of a DMF–H_2O (70:30) solution of PSBA after 27 hr by tlc (silica, EtOAc) indicated the predominant hydrolysis product to be MADDS.

4′,4‴-[*p*-Phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisformanilide (PSBF) (1).—To a solution of 5.53 g (0.020 mole) of 4′-sulfanilylformanilide (MFDDS)[1] in 300 ml of boiling EtOH was added a solution of 1.34 g (0.010 mole) of terephthalaldehyde in 50 ml of EtOH. After heating under reflux for 2 hr, the solution was concentrated to 200 ml and allowed to cool to room temperature. The precipitate was collected and dried *in vacuo* at 75° to give 5.28 g (81%) of yellow crystals, mp >300°.

Compounds **4**, **7**, and **10** were prepared in a similar manner and were crystallized from the solvents indicated in Tables I and II.

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

(23) 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.

TABLE IV

STABILITY OF PSBA IN AQUEOUS DIMETHYLFORMAMIDE

Solvent, % H_2O in DMF	PSBA half-life, hr
0	>2000
10	400
20	120
30	5.2
40	1.2
50	0.6

Procedure II. 4′,4‴-[(Tetrachloro-*p*-phenylene)bis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (2).—Solutions of 0.27 g (0.001 mole) of 2,3,5,6-tetrachloroterephthalaldehyde[13] in 10 ml of AcOH and 0.58 g (0.002 mole) of 4′-sulfanilylacetanilide (MADDS)[1] in 30 ml of AcOH were mixed and heated on a steam bath for 15 min. The precipitate which formed was collected by filtration, washed successively with AcOH and *i*-PrOH, and dried *in vacuo* at 65° to give 0.60 g (72%) of a pale yellow solid, mp 290°.

Compound **5** was prepared in the same manner, except that the AcOH was removed on a rotary evaporator, and the residue was crystallized from *i*-PrOH.

Procedure III. 4′,4‴-[*p*-Phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisheptananilide (6).—Solutions of 5.4 g (0.015 mole) of 4′-sulfanilylheptananilide[1] and 1.0 g (0.0075 mole) of terephthalaldehyde in 80 ml of *i*-AmOH were combined and heated under reflux for 2 hr. After cooling, the solution was diluted with Et_2O and the resulting pale yellow precipitate, mp 272–275°, was collected by filtration and dried.

Procedure IV. 4′,4‴-[1-Propen-1-yl-3-ylidenebis(imino-*p*-phenylenesulfonyl)]bisacetanilide Monohydrochloride Dihydrate (VIII).—To a solution of 14.5 g (0.050 mole) of 4′-sulfanilylacetanilide (MADDS)[1] in 1500 ml of MeOH there was added 6.6 ml (0.028 mole) of 1,1,3,3-tetraethoxypropane followed by 2.2 ml (0.025 mole) of concentrated HCl. After heating for 1 hr under reflux, the mixture was cooled to room temperature, and the orange crystals, mp 217–225°, were collected and dried.

Procedure V. N,N′-[Ethylenebis(oxy-*p*-phenylenemethylidyne)]bis(4-sulfanilylaniline) (VIa).—A solution of 5.96 g (0.020 mole) of 4,4′-sulfonyldianiline (DDS) in 400 ml of *i*-PrOH was added to an *i*-PrOH solution of 2.70 g (0.020 mole) of 4,4′-(ethylenedioxy)dibenzaldehyde.[16] When no immediate reaction occurred, a few crystals of *p*-toluenesulfonic acid were added and the mixture was boiled under reflux for 2 hr. The precipitate which formed was collected from the hot mixture, washed with *i*-PrOH, and dried 18 hr *in vacuo* to give 7.0 g (96%) of a pale yellow solid, mp 272–275°.

Compounds **9** and **12** were prepared in the same manner, except that EtOH was used in place of *i*-PrOH as the reaction solvent.

N,N′-(*p*-Phenylenedimethylidyne)bis[4-(N-allylsulfanilyl)aniline] (VII).—N-Allyl-4,4′-sulfonyldianiline[17] (5.75 g, 0.02 mole) and terephthalaldehyde (1.34 g, 0.01 mole) were allowed to react in 360 ml of EtOH according to procedure I. The product was obtained as yellow crystals from EtOH or MeCN, 4.5 g (67%), mp 245–249°. *Anal.* ($C_{38}H_{34}N_4O_4S_2$) C, H, N.

Acknowledgments.—The authors wish to express their appreciation to Dr. Paul E. Thompson, Dr. J. A. Waitz, Dr. M. W. Fisher, and Dr. D. H. Kaump, and coworkers of these laboratories for the antimalarial, antituberculosis, and toxicological 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. David B. Capps for assisting in some of the chemical work described herein, Dr. J. M. Vandenbelt and coworkers for the spectral determinations, and Mr. Charles E. Childs and associates for the microanalyses.