Repository Drugs. VII. N-Allylidene-4,4′-sulfonyldianiline and N-(Benzylidene- and -1-Naphthylmethylene)-N′-methylene-4,4′-sulfonyldianiline Polymers with Prolonged Antimalarial and Antileprotic Action[1]

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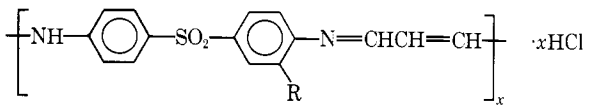
Various N-allylidene-4,4′-sulfonyldianiline polymers (Ia and b, II), N-(benzylidene- and -1-naphthylmethylene)-N′-methylene-4,4′-sulfonyldianiline polymers (IIIa and b, IV), and related substances were synthesized as potential repository antimalarial and antileprotic agents in the search for water-labile sulfones whose activation and mobilization from the depot site might not, unlike DADDS, be enzyme dependent. The N-allylidene-4,4′-sulfonyldianiline polymers were prepared from DDS, 4-sulfanilyl-*o*-toluidine, and 1,1,3,3-tetraethoxypropane in MeOH and HCl, while the N-(benzylidene- and -1-naphthylmethylene)-N′-methylene-4,4′-sulfonyldianiline polymers were synthesized from DDS and the corresponding dialdehyde in *i*-PrOH or *i*-AmOH. Among them, polymeric N-allylidene-4,4′-sulfonyldianiline hydrochloride (Ia), N-allylidene-2-methyl-4,4′-sulfonyldianiline hydrochloride (Ib), and N-benzylidene-N′-methylene-4,4′-sulfonyldianiline (IIIb), together with N,N′-[sulfonylbis(*p*-phenylenenitrilopropenylene)]bis(4-sulfanilylaniline) (II), fulfilled the above requirements and protected mice for periods of 3.5–8.5 weeks against *Plasmodium berghei* and >8 weeks against *Mycobacterium leprae*.

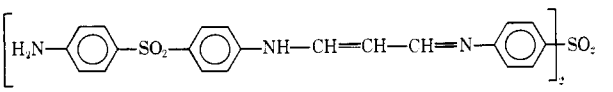
In previous papers it was reported that cycloguanil pamoate,[2-4] acedapsone,[5-13] and various 4′,4‴-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]-bisacetanilides,[14] 4′-[N-(benzylidene)sulfanilyl]anilides,[1] 4′-[N-(salicylidene)sulfanilyl]anilides,[1] and α-{[*p*-(N-alkylsulfanilyl)phenyl]imino}-4,6-dihalo-*o*-cresols[1] exhibit remarkable repository antimalarial, antileishmanial, and antileprotic properties. The present communication summarizes the results of investigations aimed toward the development of water-labile, repository DDS polymers whose activation and mobilization from the depot site might not be enzyme dependent. Several of the polymers described herein satisfied these requisites and exhibited promising repository antimalarial and antileprotic action.

The condensation of 1,1,3,3-tetraethoxypropane with 4,4′-sulfonyldianiline and 4-sulfanilyl-*o*-toluidine in MeOH and HCl afforded polymeric N-allylidene-4,4′-sulfonyldianiline hydrochloride (Ia) (90%) and N-allylidene-2-methyl-4,4′-sulfonyldianiline hydrochloride (Ib) (84%), respectively (Table I). Treatment of



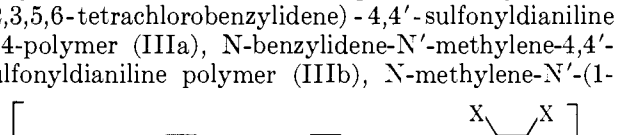
Ia, R = H
b, R = CH_3

Ia with NaOH in MeOH converted Ia to a fragment which analyzed correctly (C, H, N, S, H_2O) for N,N′-[sulfonylbis(*p*-phenylenenitrilopropenylene)]bis(4-sulfanilylaniline) monohydrate (II). Polymerization of

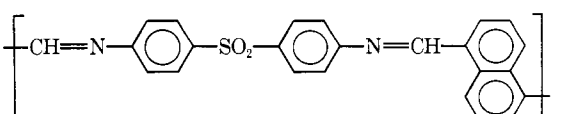


II

4,4′-sulfonyldianiline and 2,3,5,6-tetrachloroterephthalaldehyde,[15] terephthalaldehyde, 1,5-naphthalenedicarboxaldehyde,[16] and 4,4′-(ethylenedioxy)dibenzaldehyde[17] in *i*-PrOH or *i*-AmOH gave N-methylene-N′-(2,3,5,6-tetrachlorobenzylidene)-4,4′-sulfonyldianiline α,4-polymer (IIIa), N-benzylidene-N′-methylene-4,4′-sulfonyldianiline polymer (IIIb), N-methylene-N′-(1-naphthylmethylene)-4,4′-sulfonyldianiline α,5-polymer (IV), and N-methylene-N′-[*p*-(2-phenoxyethoxy)ben-



IIIa, X = Cl
b, X = H



IV

(1) Previous paper: D. F. Worth, E. F. Elslager, and A. A. Phillips, *J. Med. Chem.*, **12**, 591 (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, Z. B. Gavrilis, A. A. Phillips, and D. F. Worth, *J. Med. Chem.*, **12**, 357 (1969).

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

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

(8) (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).

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

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

(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) D. F. Clyde, Abstracts, 8th International Congresses on Tropical Medicine and Malaria, Teheran, Iran, Sept 7–15, 1968, p 1380.

(13) 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.

(14) E. F. Elslager, A. A. Phillips, and D. F. Worth, *J. Med. Chem.*, **12**, 363 (1969).

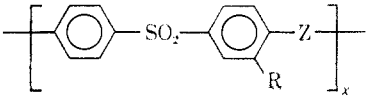
(15) 2,3,5,6-Tetrachloroterephthalaldehyde was generously supplied by Mr. Charles E. Granito, Diamond Shamrock Corp., Painesville, Ohio 44077.

(16) 1,5-Naphthalenedicarboxaldehyde 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).

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

TABLE I

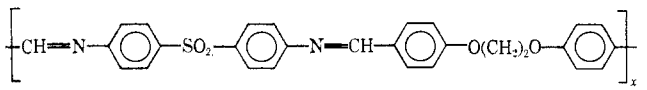
N-(BENZYLIDENE- AND -1-NAPHTHYLMETHYLENE)-N'-METHYLENE-4,4'-SULFONYLDIANILINE AND N-ALLYLIDENE-4,4'-SULFONYLDIANILINE POLYMERS[a]



No.	R	Z	Mp, °C	Yield, %	(Formula)$_x$	Analyses[19]
Ia	H	N=CHCH=CHNH	258–262 dec	90	$C_{15}H_{12}N_2O_2S \cdot HCl \cdot 0.5H_2O$	C, H, N
Ib	CH_3	N=CHCH=CHNH	257–259 dec	84	$C_{16}H_{14}N_2O_2S \cdot HCl \cdot 1.25H_2O$	C, H, N, H_2O
IIIa	H	N=CH-*p*-C_6Cl_4CH=N	>400	49	$C_{20}H_{10}Cl_4N_2O_2S \cdot 0.5H_2O$	C, H, N
IIIb	H	N=CH-*p*-C_6H_4CH=N	>400	89	$C_{20}H_{14}N_2O_2S \cdot 0.5H_2O$	C, H, N
IV	H	N=CH-1,5-$C_{10}H_6CH$=N[b]	Sinters 240	50	$C_{24}H_{16}N_2O_2S \cdot H_2O$	C, H, N, H_2O
V	H	(N=CH-*p*-$C_6H_4O)_2(CH_2)_2$	358-367 dec	77	$C_{28}H_{22}N_2O_4S \cdot 0.5H_2O$	C, H, N

[a] Compounds range from yellow to red. [b] C_6H_{10} represents naphthylene.

zylidene]-4,4'-sulfonyldianiline polymer (V), respectively (Table I), in 49–89% yield.



V

The DDS content of the polymers IIIa and b, IV, and V was measured by a uv assay (Experimental Section). These results, together with the microanalyses (Table I), indicate a nearly 1:1 ratio of DDS to aldehyde moiety. Problems associated with the insolubility and instability of these polymers in suitable solvents precluded the use of solution methods for molecular weight determination.

The N-allylidene-4,4'-sulfonyldianiline and N-(benzylidene- and -1-naphthylmethylene)-N'-methylene-4,4'-sulfonyldianiline polymers 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,[1-4,6,7,14] 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.

The N-allylidene-4,4'-sulfonyldianiline hydrochloride polymer (Ia) exhibited very long acting repository antimalarial effects. A single, subcutaneous 400-mg/kg dose of Ia protected 50% of the mice for approximately 8.5 weeks against challenge with *P. berghei*. Polymeric N-allylidene-2-methyl-4,4'-sulfonyldianiline hydrochloride (Ib), N,N'-[sulfonylbis(*p*-phenylenenitrilopropenylene)]bis(4-sulfanilylaniline) (II), and the N-benzylidene-N'-methylene-4,4'-sulfonyldianiline polymer (IIIb) protected mice from challenge with *P. berghei* for approximately 3.5–4 weeks, a period intermediate between the short-acting DDS and the very long acting DADDS and PSBF.[10,14] These results suggested that polymers Ia and b, II, and IIIb should provide higher blood levels than DADDS or PFBF and still afford protection for reasonable periods of time. By contrast, the N-methylene-N'-[*p*-(2-phenoxyethoxy)benzylidene]-4,4'-sulfonyldianiline polymer (V) failed to protect all of the mice for even 1 week.

Because of the over-all interest in polymers Ia, II, and IIIb as repository antimalarial and antileprotic agents, these drugs were also supplied to Dr. Charles C. Shepard, Communicable Disease Center, Atlanta, Ga., for evaluation against *Mycobacterium leprae* in mice. Each polymer was completely suppressive when administered subcutaneously in single 200–400-mg/kg doses in BBCO at 2-month intervals.

Comparative antimalarial, antileprotic, and metabolic data on DDS, MADDS, DADDS, PSBA, and three DDS polymers (Ia, II, and IIIb) in mice and rats is presented in Table II.[8a,10] The duration of protection against challenge with *P. berghei* afforded by a single subcutaneous 400-mg/kg dose of these polymers ranged from 3.5 to 8.5 weeks. 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 *P. berghei*.[8b] The pattern of urinary excretion in rats also was intermediate between DDS and DADDS. These results imply that polymers Ia, II, and IIIb might provide a relatively more intense, albeit less prolonged, chemotherapeutic effect than an equivalent dose of DADDS or PSBF, and be much safer drugs than DDS.

Experimental Section[18,19]

Uv Assay for DDS Content of Polymers IIIa and b, IV, and V.—A sample of the polymer was dissolved in 0.5 *N* HCl in MeOH with warming if necessary. After solution was complete, an aliquot was removed and an appropriate dilution was made into MeOH containing sufficient KOH to neutralize the acid. The spectrum of the solution, which now contained free DDS, was determined. The DDS concentration was then obtained using an E_1^1 of 1180 at 295 mμ, except for V which exhibited relatively strong absorption from the aldehyde residue where readings at 310 mμ were used (Table III). Polymers Ia and b could not be assayed in this fashion due to their relative stability in the methanolic HCl.

N-Allylidene-4,4'-sulfonyldianiline Hydrochloride Polymer (Ia).—To a solution of 24.8 g (0.10 mole) of 4,4'-sulfonyldianiline (DDS) in 1 l. of MeOH was added 24 ml (0.10 mole) of 1,1,3,3-tetraethoxypropane followed by 8.6 ml (0.10 mole) of concentrated HCl. After heating under reflux for 20 min the orange precipitate was collected by filtration and washed thoroughly with MeOH.

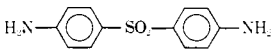
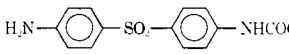
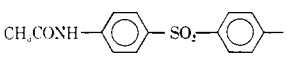
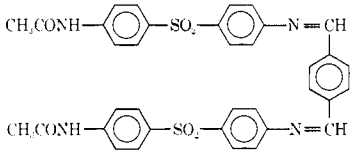
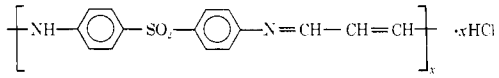
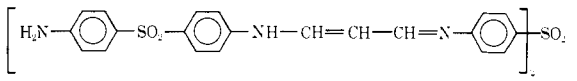
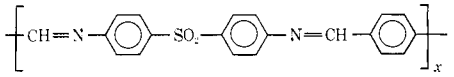
N-Allylidene-2-methyl-4,4'-sulfonyldianiline hydrochloride polymer (Ib) was prepared from 4-sulfanilyl-*o*-toluidine and

(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.

TABLE II

COMPARATIVE ANTIMALARIAL, ANTILEPROTIC, AND METABOLIC DATA ON DDS, MADDS, DADDS, PSBA, AND SELECTED 4,4′-SULFONYLDIANILINE POLYMERS[8a,10]

Compd	Structure	Weeks mice protected *P. berghei*[a]	Weeks mice protected *M. leprae*[b]	Rats[c] Urinary excretion % excreted in 30 days	Rats[c] Urinary excretion Estd half-life, days	Rats[c] Peak blood level, μg/ml	Rats[c] 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
Ia		8.5	>8	32	25		
II		3.5	>8	34	39		
IIIb		4	>8	50	30		

[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.

TABLE III

UV ASSAY FOR DDS CONTENT OF POLYMERS

Polymer	DDS content, % Calcd	DDS content, % Found
IIIa	51.3	49.7
IIIb	69.8	72.4
IV	59.9	65.5
V	50.5	48.2

1,1,3,3-tetraethoxypropane according to the procedure used for compound Ia.

N,N′-[Sulfonylbis(*p*-phenylenenitrilopropenylene)]bis(4-sulfanilylaniline) Monohydrate (II).—The N-allylidene-4,4′-sulfonyldianiline hydrochloride polymer (Ia) (19.0 g, 0.058 mole) was suspended in 1 l. of H_2O containing 55 ml of 1 *N* NaOH, and stirred in a blender. The solid was filtered from the alkaline mixture, washed well with H_2O, and dried *in vacuo* at 50° to give 15.5 g. This bright yellow powder sintered at 220°, but did not melt <300°. *Anal.* ($C_{42}H_{36}N_6O_6S_3 \cdot H_2O$) C, H, N, S, H_2O.

N-Methylene-N′-(2,3,5,6-tetrachlorobenzylidene)-4,4′-sulfonyldianiline α,4-Polymer (IIIa).—A mixture of 2.0 g (0.0074 mole) of 2,3,5,6-tetrachloroterephthalaldehyde[15] and 2.0 g (0.0081 mole) of 4,4′-sulfonyldianiline (DDS) in 100 ml of *i*-AmOH was boiled under reflux for 2 hr. The yellow precipitate, which began to form after heating for 45 min, was collected by filtration and dried.

N-Benzylidene-N′-methylene-4,4′-sulfonyldianiline Polymer (IIIb).—To a stirred, boiling solution of 12.4 g (0.050 mole) of 4,4′-sulfonyldianiline (DDS) in 400 ml of *i*-PrOH was added a solution of 6.7 g (0.050 mole) of terephthalaldehyde in 300 ml of boiling *i*-PrOH. In about 30 sec a yellow precipitate began to form. After heating under reflux for 2 hr, the precipitate was collected by filtration from the hot reaction mixture and dried *in vacuo* at 65° for 18 hr.

N-Methylene-N′-(1-naphthylmethylene)-4,4′-sulfonyldianiline α,5-Polymer (IV).—A solution of 0.50 g (0.0034 mole) of 4,4′-sulfonyldianiline (DDS) and 0.84 g (0.0034 mole) of 1,5-naphthalenedicarboxaldehyde[15] in 150 ml of *i*-PrOH was boiled for 3 hr while 75 ml of solvent was removed by distillation. At this time, no precipitation had appeared and tlc (silica gel, EtOAc) showed the presence of both starting materials. Addition of a trace of *p*-toluenesulfonic acid caused the rapid formation of a yellow precipitate. After 10 min this was collected by filtration from the hot reaction mixture, washed with *i*-PrOH, and dried *in vacuo* at 85°.

N-Methylene-N′-[*p*-(2-phenoxyethoxy)benzylidene]-4,4′-sulfonyldianiline Polymer (V).—A solution of 2.5 g (0.01 mole) of 4,4′-sulfonyldianiline and 2.7 g (0.01 mole) of 4,4′-(ethylenedioxy)dibenzaldehyde[17] in 350 ml of *i*-PrOH was boiled under reflux. When, after 20 min, no precipitation had occurred, a few crystals of *p*-toluenesulfonic acid were added and heating was continued for 2 hr. The solid was collected from the hot mixture and dried.

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