Notes

Antimalarial and Antischistosomal Agents. N,N″-[Sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N′,N′-dialkylalkylenediamines)[1]

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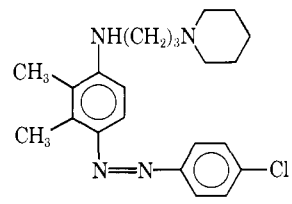
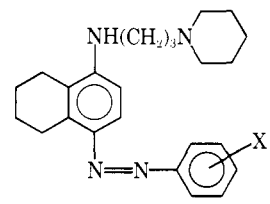
In previous communications from these laboratories, various N-mono- and N,N-dialkyl-N′-(4-arylazo- and 4-heterocyclic azo-1-naphthyl)alkylenediamines,[2-4] bis-(4-arylazo-1-naphthylamines),[5] N-(dialkylaminoalkyl)-4-nitroso-1-naphthylamines,[6] and N-(mono- and dialkylaminoalkyl)-1,4-naphthalenediamines[7] were reported to have strong therapeutic effects against *Schistosoma mansoni* in experimental animals.[2-7] Moreover, certain 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo- and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines are highly active against *Mycobacterium tuberculosis* $H_{37}Rv$ and *Mycobacterium lepraemurium in vitro* and in mice.[8,9]

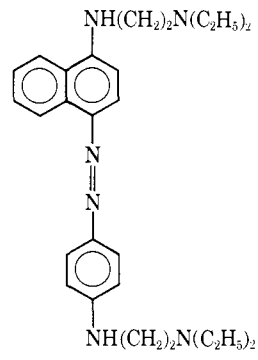
Because of the seriousness of the situation created by the possibility of widespread resistance of *Plasmodium falciparum* to the 4-aminoquinolines and the resulting urgent need for new types of fast-acting suppressive antimalarial drugs,[10] representative compounds from the above chemical types were supplied to Dr. Paul E. Thompson and co-workers of these laboratories for evaluation against *Plasmodium berghei* in mice.[11] The drugs were administered continuously in the diet for 6 days to mice infected with a normal drug-sensitive strain of *P. berghei*. Results are expressed both in terms of the SD_{90} (daily dose required for 90% suppression of the parasitemia) and the quinine equivalent Q (the ratio of the SD_{90} of quinine to the SD_{90} of the test substance under comparable experimental conditions). Representative compounds from each of the aforesaid chemical types exhibited antimalarial activity against *P. berghei* in the mouse. With the exception of the *p*-(4-amino-1-naphthylazo)benzenesulfonamides, which might be expected to undergo reductive scission *in vivo*[7] and release a sulfonamide moiety having antimalarial activity *per se*,[10] the most active compounds tested were 1-{3-[4-(*p*-chlorophenylazo)-2,3-xylidino]propyl}-piperidine (I)[8] (SD_{90} = 58 mg/kg/day, Q = 1.3), 1-{3-[4-(*p*-chlorophenylazo)-5,6,7,8-tetrahydro-1-naphthylamino]propyl}piperidine (IIa)[8] (SD_{90} = 49 mg/kg/day, Q = 1.5), 1-(3-{[4-(3,5-dichlorophenylazo)-5,6,7,8-tetrahydro-1-naphthyl]amino}propyl)piperidine (IIb)[8] (SD_{90} = 88 mg/kg/day, Q = 0.9), and N′-{*p*-[4-(2-diethylaminoethylamino)-1-naphthylazo]phenyl}-N,N-diethylethylenediamine (III)[4] (SD_{90} = 70 mg/kg/day, Q = 1.1). Among the other structure types, N,N″-



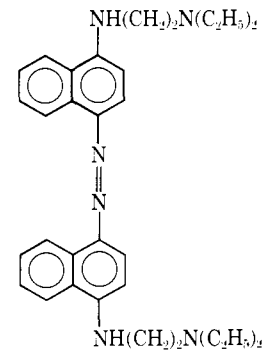
I



IIa, X = 4-Cl
b, X = 3,5-Cl_2

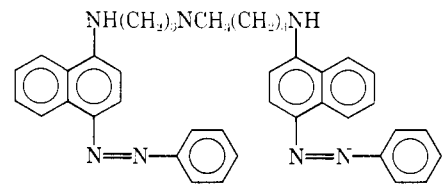


III

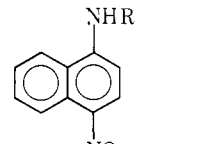


IV

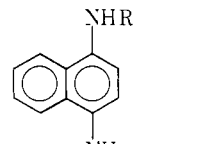
(azodi-1,4-naphthylene)bis(N′,N′-diethylethylenediamine) (IV),[4] N,N′-[methyliminobis(trimethylene)]-bis(4-phenylazo-1-naphthylamine) (V),[5] N,N-di-



V



VIa, R = $(CH_2)_3N(CH_3)_2$
b, R = $CH_2CCH_2N(C_2H_5)_2$ with $(CH_3)_2$



VIIa, R = $(CH_2)_3N(C_2H_5)_2$
b, R = $(CH_2)_3N$

methyl-N′-(4-nitroso-1-naphthyl)-1,3-propanediamine (VIa),[6] N,N-diethyl-2,2-dimethyl-N′-(4-nitroso-1-naph-

(1) This is paper XV of a series relating to antimalarial substances. For paper XIV, see E. F. Elslager and N. F. Haley, *J. Heterocyclic Chem.*, **6**, 105 (1969). This is paper XII of a series on synthetic schistosomicides. For paper XI, see E. F. Elslager and N. F. Haley, *ibid.*, **6**, 105 (1969).

(2) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *J. Med. Chem.*, **6**, 217 (1963).

(3) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).

(4) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, *ibid.*, **9**, 378 (1966).

(5) E. F. Elslager, D. B. Capps, D. H. Kurtz, and D. F. Worth, *ibid.*, **11**, 1201 (1968).

(6) L. M. Werbel, E. F. Elslager, and D. F. Worth, *ibid.*, **11**, 950 (1968).

(7) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, and P. E. Thompson, *ibid.*, **7**, 487 (1964).

(8) L. M. Werbel, E. F. Elslager, M. W. Fisher, Z. B. Gavrilis, and A. A. Phillips, *ibid.*, **11**, 411 (1968).

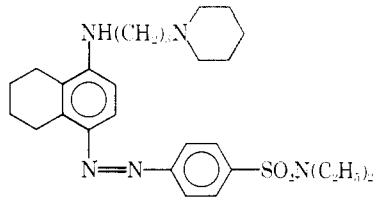
(9) Y. T. Chang, *Antimicrobial Agents Chemotherapy 1965*, 465 (1966).

(10) 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.

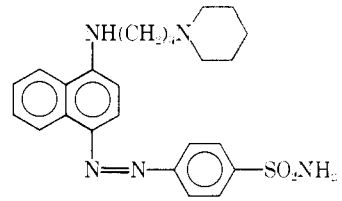
(11) For a description of the test method, see P. E. Thompson, A. Bayles, and B. Olszewski, *Exp. Parasitol.*, in press.

thyl)-1,3-propanediamine (VIb),[6] N-(3-diethylaminopropyl)-1,4-naphthalenediamine (VIIa),[7] and 1-[3-(4-amino-1-naphthylamino)propyl]pyrrolidine (VIIb),[7] when administered to mice in daily doses ranging from 70 to 272 mg/kg for 6 days, produced a significant reduction in parasitemia (49–92%) among each treated group, but were not potent enough to warrant a precise determination of the SD_{90} dose.

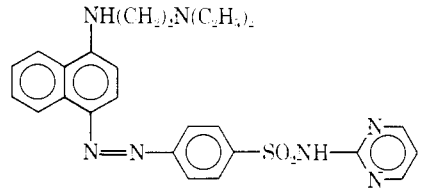
Antimalarial potency among the naphthylamines was markedly enhanced by the introduction of a sulfonamide function, and N,N-diethyl-*p*-[5,6,7,8-tetrahydro-4-(3-piperidinopropylamino)-1-naphthylazo]benzenesulfonamide (VIII)[8] (SD_{90} = 19 mg/kg/day), *p*-[4-(3-piperidinopropylamino)-1-naphthylazo]benzenesulfonamide (IX)[4] (SD_{90} = 8.5 mg/kg/day), and *p*-[4-(2-diethylaminoethylamino)-1-naphthylazo]-N-(2-pyrimidinyl)-benzenesulfonamide (X)[4] (SD_{90} = <6.0 mg/kg/day) were 3.9, 8.8, and >12 times as potent as quinine, respectively. This increase in potency is consistent



VIII



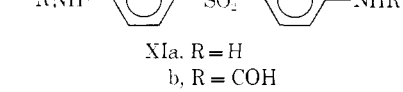
IX



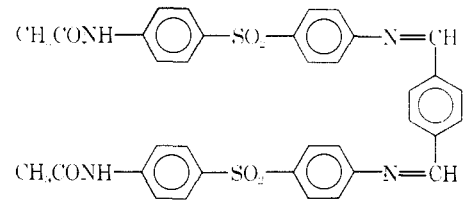
X

with the anticipated contribution of the sulfonamide moiety assuming reductive scission of the molecule.

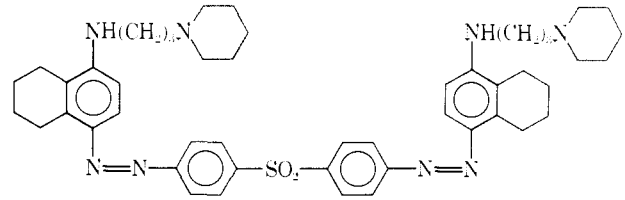
In view of the antimalarial activity inherent among these N,N-dialkyl-N′-1-naphthylalkylenediamines and the current clinical interest in the prophylactic and repository antimalarial properties of 4,4′-sulfonyldianiline (dapsone, DDS) (XIa),[10] 4′,4‴-sulfonylbisformanilide (DFDDS) (XIb),[12] 4′4‴-sulfonylbisacetanilide (acedapsone, DADDS) (XIc),[12,13] and 4′,4‴-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (PSBA) (XII),[14] it was of interest to synthesize certain N,N″-[sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N′,N′-dialkylalkylenediamine) prototypes (XIII, XIV) that incorporate both structural features into one molecule. It was anticipated that such



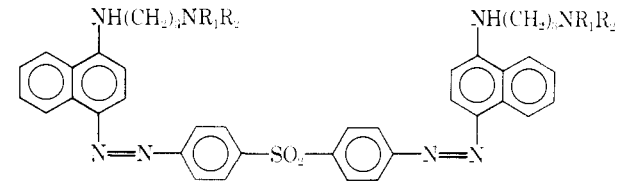
XIa, R = H
b, R = COH
c, R = COCH3

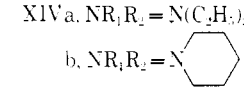


XII



XIII



XIVa, $NR_1R_2 = N(C_2H_5)_2$
b, NR_1R_2 = 

compounds might undergo reductive scission *in vivo* releasing both active moieties, thereby affording broader action against drug-resistant strains than either moiety alone. 1,1′-{Sulfonylbis[*p*-phenyleneazo(5,6,7,8-tetrahydro-1,4-naphthylene)iminotrimethylene]}dipiperidine (XIII), N,N″-[sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N′,N′-diethyl-1,3-propanediamine) (XIVa), and 1,1′-[sulfonylbis(*p*-phenyleneazo-1,4-naphthyleneiminotrimethylene)]dipiperidine (XIVb) were prepared in 33–69% yield by coupling tetrazotized 4,4′-sulfonyldianiline (DDS) (XIa)[12] with 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine,[8] N,N-diethyl-N′-1-naphthyl-1,3-propanediamine,[15] and 1-[3-(1-naphthylamino)propyl]piperidine,[15] respectively, in aqueous HCl.

Compounds XIII, XIVa, and XIVb showed marked therapeutic activity against the normal drug-sensitive line of *P. berghei* in the mouse. 1,1′-{Sulfonylbis[*p*-phenyleneazo(5,6,7,8-tetrahydro-1,4-naphthylene)-iminotrimethylene]}dipiperidine (XIII) (SD_{90} = 0.9 mg/kg/day), N′,N″-[sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N′,N′-diethyl-1,3-propanediamine) (XIVa) (SD_{90} = 1.1 mg/kg/day), and 1,1′-[sulfonylbis-(*p*-phenyleneazo-1,4-naphthyleneiminotrimethylene)]-dipiperidine (XIVb) (SD_{90} = <91 mg/kg/day) were 83, 68, and >1 times as potent as quinine, respectively. By contrast, the daily SD_{90} of XIII and XIVa against a line of *P. berghei* made completely resistant (>600-fold) to DDS was >80 and >18 mg/kg, respectively. Therefore, hopes that such compounds might possess significantly broader action against DDS-resistant lines of *P. berghei* were not realized.

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

(13) E. F. Elslager and D. F. Worth, *Nature*, **206**, 630 (1965).

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

(15) L. M. Werbel, D. B. Capps, E. F. Elslager, W. Pearlman, F. W. Short, E. A. Weinstein, and D. F. Worth, *ibid.*, **6**, 637 (1963).

The N,N′′-[sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N′,N′-dialkylalkylenediamines) (XIII, XIVa, and XIVb) were also tested in mice against a Puerto Rican strain of *S. mansoni*.[16] Drugs were given in a powdered diet for 14 days and drug amounts are expressed as free base. Compounds XIII, XIVa, and XIVb were highly active and effected a 53–100% reduction of live schistosomes in mice at doses ranging from 86 to 364 mg/kg/day.

Against representative bacteria *in vitro*, including *Staphylococcus aureus* (UC-76), *Pseudomonas aeruginosa* (28), *Mycobacterium tuberculosis* ($H_{37}Rv$), *Escherichia coli* (Vogel), *Diplococcus pneumoniae*, *Streptococcus pyogenes* (C203), *Proteus mirabilis* (MGH-1), and *Salmonella typhimurium* (V-31),[8] compound XIII caused complete inhibition of *M. tuberculosis* $H_{37}Rv$ at a concentration of 20 μg/ml and XIVa caused complete inhibition of the following organisms: *S. aureus* (UC-76), 20 μg/ml; *M. tuberculosis* ($H_{37}Rv$), 20 μg/ml; *D. pneumoniae*, 1.25 μg/ml; and *S. pyogenes* (C203), 0.63 μg/ml. 1,1′-{Sulfonylbis[*p*-phenyleneazo(5,6,7,8-tetrahydro-1,4-naphthylene)iminotrimethylene]}dipiperidine (XIII) was inactive against *M. tuberculosis* $H_{37}Rv$ in mice when administered at 0.04 (45 mg/kg/day) and 0.25% (142 mg/kg/day) in the diet for 7 days.[8]

Experimental Section[17,18]

1,1′-{Sulfonylbis[*p*-phenyleneazo(5,6,7,8-tetrahydro-1,4-naphthylene)iminotrimethylene]}dipiperidine (XIII).—A solution of 12.4 g (0.05 mole) of 4,4′-sulfonyldianiline (DDS)[12] in 800 ml of H_2O and 17 ml of concentrated HCl was cooled to 0° and the amine was tetrazotized by the slow, portionwise addition of 6.9 g (0.1 mole) of $NaNO_2$ in 100 ml of cold H_2O. The mixture was stirred at 0° for 15 min and then added at 0–5° to a solution of 27.2 g (0.1 mole) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]-propyl}piperidine[8] in a mixture of 200 ml of H_2O and 7.2 ml of concentrated HCl. The mixture was stirred for 2 hr at 0–5° and made alkaline with 5% NaOH. The crude product was collected by filtration, washed (H_2O), and dried. Crystallization from DMF afforded 28.0 g (69%) of red crystals, mp 180–186°. *Anal.* ($C_{48}H_{62}N_8O_2S \cdot 0.25H_2O$) C, H, N.

The base (5.0 g, 0.006 mole) was dissolved in DMF and treated with an excess of an *i*-PrOH–HCl mixture. Upon cooling, the dark purple HCl salt precipitated. The salt was collected by filtration and dried *in vacuo* at 60° for 3 days. The product was thus obtained as the tetrahydrochloride hexahydrate, 5.4 g (85%), mp 180° dec. *Anal.* ($C_{48}H_{62}N_8O_2S \cdot 4HCl \cdot 6H_2O$) C, H, Cl^-, N.

N,N′′-[Sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N′,N′-diethyl-1,3-propanediamine) Tetrahydrochloride (XIVa).—4,4′-Sulfonyldianiline (DDS)[12] (6.2 g, 0.025 mole) was tetrazotized and coupled with 12.8 g (0.05 mole) of N,N-diethyl-N′-1-naphthyl-1,3-propanediamine[15] according to the procedure for XIII. The HCl salt of the product (XIVa) was obtained as deep green crystals from DMF–*i*-PrOH–HCl, mp 290°, yield 13.6 g (52%). *Anal.* ($C_{46}H_{54}N_8O_2S \cdot 4HCl \cdot 6H_2O$) C, H, Cl^-, N.

1,1′-[Sulfonylbis(*p*-phenyleneazo-1,4-naphthyleneiminotrimethylene)]dipiperidine (XIVb).—4,4′-Sulfonyldianiline (DDS)[12] (6.2 g, 0.025 mole) was tetrazotized and coupled with 13.4 g (0.05 mole) of 1-[3-(1-naphthylamino)propyl]piperidine[15] according to the procedure for XIII. The product (XIVb) was obtained as dark red-brown crystals from DMA–MeCN, mp 160–163°, yield 6.8 g (33%). *Anal.* ($C_{48}H_{54}N_8O_2S \cdot 0.5H_2O$) C, H, N.

Acknowledgments.—The authors express their appreciation to Dr. Paul E. Thompson, Dr. M. W. Fisher, and coworkers of these laboratories for the antiparasitic and antibacterial evaluation of these compounds. We also thank Dr. J. M. Vandenbelt and coworkers for the spectral studies and Mr. Charles E. Childs and associates for the microanalyses.

(16) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1962).

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

(18) 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.

2-(Alkyl- and Arylamino)-5-nitrothiazole Derivatives with Antiamebic, Antitrichomonal, and Antimalarial Properties[1]

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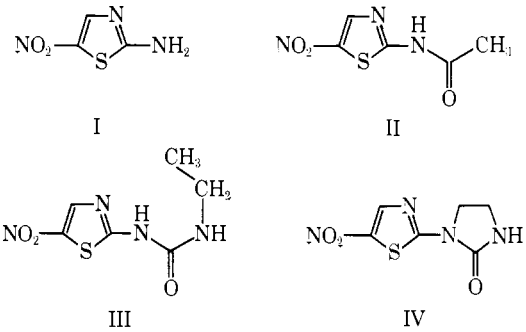
Numerous 2-amino-5-nitrothiazole derivatives exhibit antiamebic,[2,3] antihistomonal,[4] antitrichomonal,[3,5] and antischistosomal[3] properties. Among them, 2-amino-5-nitrothiazole (enheptin) (I), 2-acetamido-5-nitrothiazole (aminitrozole) (II), and 1-ethyl-3-(5-nitro-2-thiazolyl)urea (nithiazide) (III) have been employed



I II III IV

in the control of histomoniasis (blackhead) in turkeys and other domestic fowls caused by *Histomonas meleagridis*. Aminitrozole has also been used for the oral treatment of human trichomoniasis due to *Trichomonas vaginalis*, and 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (niridazole) (IV) is effective against amebiasis and schistosomiasis in man.

Most of the synthetic work on 2-amino-5-nitrothiazole derivatives as potential antiprotozoal and antischistosomal agents[2–5] has dealt with amide and urea analogs of aminitrozole, nithiazide, and niridazole, and relatively few simple 2-(alkyl- and arylamino)-5-nitro-

(1) This is paper IX of a series on synthetic amebicides; for paper VIII, see E. F. Elslager, F. W. Short, and F. H. Tendick, *J. Heterocyclic Chem.*, **5**, 599 (1968). This is paper XVI of a series relating to antimalarial substances; for paper XV, see E. F. Elslager and A. A. Phillips, *J. Med. Chem.*, **12**, 519 (1969).

(2) For a recent review, see E. F. Elslager in "Medicinal Chemistry," A. Burger, Ed., 3rd ed, Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1969.

(3) 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.

(4) For a recent review, see L. P. Joyner, S. F. M. Davies, and S. B. Kendall in "Experimental Chemotherapy," Vol. I, R. J. Schnitzer and F. Hawking Ed., Academic Press, New York, N. Y., 1963, pp 333–346.

(5) For a recent review, see R. J. Schnitzer, ref 4, pp 289–321.