Anal. ($C_8H_{14}N_2O$) N. A glpc analysis indicated a purity of 97%. A mixture of 46.4 g of the above nitrile, 350 ml of 23% (w/w) of NH_3 in MeOH, and 5–10 g of Ra Ni under H_2 at an initial pressure of 57.2 kg/cm² was heated to 100° for 8 hr. Removal of the catalyst and fractionation of the filtrate gave 36 g (76%) of oil, bp 99–100° (0.3 mm), $n^{25.2}D$ 1.5046. *Anal.* ($C_8H_{18}N_2O$) C, H, N.

Preparation of Final Products. General Procedure.—A mixture of 4,7-dichloroquinoline (Winthrop Laboratories) and 2 molar equiv of amine was stirred under N_2 in an oil bath at 150–160° for 4–10 hr. The product was taken up in dilute HCl and the pH was adjusted to *ca.* 7 with concentrated NH_4OH. The mixture was extracted twice with Et_2O which was discarded. The aqueous portion was made strongly basic with 35% NaOH solution and the oily product was extracted (Et_2O). Removal of solvent and unreacted amine was accomplished by heating under reduced pressure, finally at 100° (0.1 mm). The aminoquinolines were isolated as the free bases or as salts (Table II).

TABLE II

Compd	Salt	Mp, °C	Formula	Analyses
2a	$2H_3PO_4$	272–275 dec	$C_{18}H_{24}ClN_3 \cdot 2H_3PO_4$	N, Cl
2b		125.5–126.5	$C_{17}H_{22}ClN_3$	N, Cl
2c	$2HCl \cdot H_2O$	265–268	$C_{17}H_{22}ClN_3O \cdot 2HCl \cdot H_2O$	N, Cl, H_2O

Antimalarials Related to 2-Bromo-4,5-dimethoxy-N,N′-bis(diethylaminoethyl)aniline. Piperazine Modifications[1,2]

EUGENE L. STOGRYN

Esso Research and Engineering Company, Government Research Laboratory, Linden, New Jersey 07036

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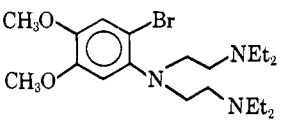
It has recently been reported that 2-bromo-4,5-dimethoxy-N,N′-bis(diethylaminoethyl)aniline (I) is effective against the exo-erythocytic stages of *Plasmodium cathemerium* in canaries.[3] From an evaluation of



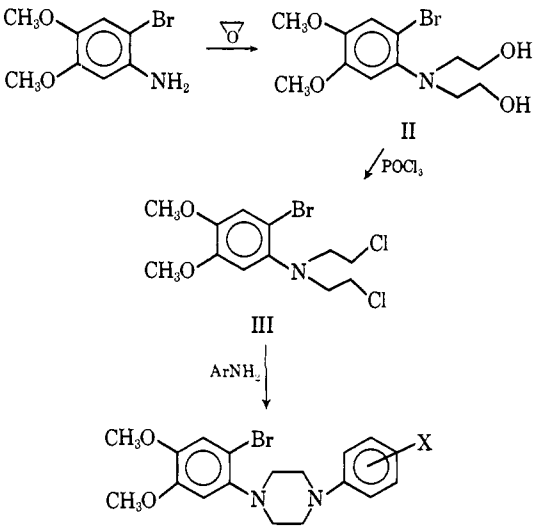
I

I against *Plasmodium cynamolgi* in rhesus monkey Schmidt[4] concluded that I shows considerable promise as a radical curative agent. This revived interest in the aminopyrocatechol[5] class of antimalarials prompted us to investigate structural modifications of the basic side chain.

Schoenhofer's[6] work demonstrated that the basic side chain must conform to the rigid structural features depicted by I. We decided to synthesize and evaluate piperazines and spiropiperazinium salts, related to I, as radical departures from the already studied aminopyrocatechols.

Chemistry.—Synthesis of the modifications described in this paper were realized by the reactions in Scheme I. The key intermediate to this scheme, 2-bromo-4,5-dimethoxyaniline,[7] can be prepared by the bromination of 3,4-dimethoxyacetanilide. Since this procedure did not appear to be capable of yielding substantial quantities of the desired material as the free base, several alternate routes were examined.[8] The best technique found for the preparation of 2-bromo-4,5-dimethoxyaniline was the reduction of the corresponding nitro compound by the reducing system N_2H_4–Raney Ni, after the procedure of Leggetter and Brown.[9] Yields of 85% of the desired arylamine, as the free base, were consistently obtained, even on large-scale reductions.

SCHEME I



Hydroxethylation of 2-bromo-4,5-dimethoxyaniline with ethylene oxide by the procedure of Freifelder and Stone[10] gave only the monoalkylated product. Extending the reaction to 3 days at 90° gave 90% of II. Careful control of reaction conditions and stoichiometry was necessary to suppress the formation of polyethylene oxides, the presence of which made purification of II difficult. $SOCl_2$[11a] or preferrably $POCl_3$[11b] was used to convert II to the nitrogen mustard III. This compound (III) was obtained in 89% yield as a nondistillable viscous oil. To circumvent the laborious purification procedure of III we attempted to synthesize a variation of III that was a solid at room temperature. Synthesis of III wherein chlorine was replaced by bromine, mesylate, tosylate, or brosylate did not yield a solid precursor to IV.

Reaction of the appropriately substituted anilines with III, according to the procedure of Davis and Ross[12] gave modest yields of the N-phenylpiperazines listed in Table I. The *m*- and *p*-nitroanilines failed to react with III. Treatment of bis(chloroethyl)-*m*-nitroaniline

(1) This work was supported by the U. S. Army Medicinal Research and Development Command under Contract No. DA-49-193-MD-2900. This is Contribution No. 413 from the Army Research Program on Malaria.

(2) Presented in part at the symposium on The Resistant Malaria Problem before The Medicinal Chemistry Section, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(3) L. J. Bruce-Chwatt, *Trans. Roy. Soc. Trop. Med. Hyg.*, **59**, 105 (1965).

(4) L. H. Schmidt, *et al.*, *Bull. World Health Organ.*, **34**, 783 (1966).

(5) W. Schulemann and W. Kropp, U. S. Patent 1,757,394 (1930).

(6) F. Schoenhofer, *FIAT, Rev. Ger. Sci.*, PB-85033:33 (1939–1946).

(7) J. L. Simonsen and M. G. Rau, *J. Chem. Soc.*, 782 (1918).

(8) Direct bromination of 4-aminoveratrole gave intensely colored materials which were difficult to purify. Catalytic hydrogenation of 4-bromo-5-nitroveratrole were intolerably slow or under more drastic conditions complicated by extensive loss of bromine accompanying reduction of the nitro group.

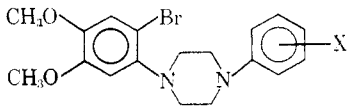
(9) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **38**, 2363 (1960).

(10) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 1477 (1961).

(11)(a) W. E. Hanby and H. N. Rydon, *J. Chem. Soc.*, 513 (1947); (b) W. C. Ross, *ibid.*, 183 (1949).

(12) W. Davis and W. C. Ross, *ibid.*, 2831 (1949).

TABLE I



X	Yield, %	Mp, °C	Formula	Analyses[a]	Antimalarial act.,[b] Δ survival time, days — 10 mg/kg	160 mg/kg	640 mg/kg
H	31	121.5–122.5	$C_{18}H_{21}BrN_2O_2$	C, H, N	0.1	0.1	0.1
p-CH_3	42	129–131	$C_{19}H_{23}BrN_2O_2$	N	0.3	0.5	0.5
p-Cl	19	147–149	$C_{18}H_{20}BrClN_2O_2$	N	0	0.2	0.2
p-F	20	148–150	$C_{18}H_{20}BrFN_2O_2$	N, Br, F	0.1	0.1	0.1
p-OCH_3	40	122–124	$C_{19}H_{23}BrN_2O_3$	N, Br	0.1	0.3	0.3
p-SCH_3	38	128.5–130	$C_{19}H_{23}BrN_2O_2S$	N, Br, S	0.1	0.5	0.5
m-CH_3	48	134–136.5	$C_{19}H_{23}BrN_2O_2$	C, N[c]	0	0.2	0.2
m-Cl	9	116–117	$C_{18}H_{20}BrClN_2O_2$	N	0.1	0.3	0.5
m-F	29	145–147	$C_{18}H_{20}BrFN_2O_2$	C, H, N	0.1	0.3	0.5
m-OCH_3	30	135–137	$C_{19}H_{23}BrN_2O_3$	N	0.3	0.3	0.5
2-CH_3-4,5-$(OCH_3)_2$	5	201.5–203	$C_{21}H_{27}BrN_2O_4$	C, H, N	0	0	0
I					0.2	0.4	1.8
Dimeplasmin					2.1	3.4	(5/5)

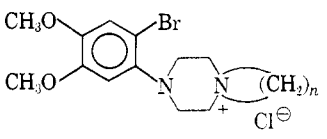
[a] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value. [b] Mice were treated 3 days postinfection subcutaneously with a single dose of the compound being screened at the dose levels shown. The change in survival time compared to the test rodent is an indication of activity against *P. berghei*. Death to the test rodents before the control is indicative of toxicity (expressed in parentheses as deaths/test mice). For a detailed discussion of this activity screen see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). [c] C: calcd, 58.31; found, 58.80. N: calcd, 7.16; found, 7.71.

with 4-bromo-5-aminoveratrole also failed to yield the N-(*m*-nitrophenyl)piperazine member of this series.

The basic side chain of I was further varied by preparation of piperazinium salts having the spiro configuration. Synthesis of these compounds was accomplished in moderate yields by treating III with the appropriate secondary amine, in THF.

Biological Activity.—The compounds of type IV and V were tested[13] for antimalarial activity against mice at the indicated dose levels. Results of these tests are listed in Tables I and II. Mouse screen test data on I

TABLE II



V

n	Yield, %	Mp, °C	Formula	Analyses[a]	Antimalarial act.,[b] survival time, days, at 40 mg/kg
4	58	275–280 dec	$C_{16}H_{24}BrClN_2O_2$	C, H, N	...
5	32	275–280 dec	$C_{17}H_{26}BrClN_2O_2$	H, N, O	(5/5)
6	50	299–300	$C_{18}H_{28}BrClN_2O_2$	H, N	(3/5)

[a] See footnote *a* in Table I. [b] For an explanation of the activity screen and the significance of the numbers, see footnote *b* in Table I.

and dimeplasmin are included in Table I for purposes of comparison.

In view of the low order of activity of I against *Plasmodium berghei* compounds IV and V were also evaluated for activity against chicks infected with *Plasmodium gallinaceum*.[14] None of the structures prepared in this study showed activity in this avian activity screen.

(13) Testing was carried out by Dr. L. Rane of the University of Miami, Miami, Fla.

(14) Avian antimalarial activity screens were carried out as part of the Walter Reed Army Institute of Research malaria program. I was active at the 40-mg/kg level and curative without toxic deaths at the 80- and 640-mg/kg levels against chicks infected with *P. gallinaceum*. Dimeplasmin was inactive at the 240-mg/kg level.

Experimental Section

2-Bromo-4,5-dimethoxyaniline.—To a refluxing well-stirred solution of 400 g of 4-bromo-5-nitroveratrole[15] in 6 l. of MeOH was added about 10 g of Raney nickel. Hydrazine hydrate (67%) (250 g) was then dropped into the solution at a rate so that the gas evolution was not too vigorous. After about half of the hydrazine had been added, an additional 10 g of Raney nickel was added. During the course of reduction, the characteristic yellow color of the nitro compound gradually faded. Stirring and refluxing was continued until the froth was essentially colorless (3–4 hr). Cooling, filtration, and stripping off MeOH under reduced pressure left a light brown solid. A minimum of CH_2Cl_2 was used to dissolve this solid. Pentane (about one-fourth the volume of CH_2Cl_2) was gradually added with swirling. This resulted in the precipitation of dark impurities. Decanting the solution, adding it to a large volume of pentane, and cooling gave 2-bromo-4,5-dimethoxyaniline as white to pale yellow needles, mp 52°, in 85% yield.

2-Bromo-4,5-dimethoxy-N,N′-bishydroxyethylaniline (II).—2-Bromo-4,5-dimethoxyaniline (30 g, 0.13 mole) and 22.7 g (0.52 mole) of ethylene oxide were heated in a Fisher–Porter glass pressure reactor at 90° for 3 days. The reactor was cooled and opened, and the excess ethylene oxide was stripped off. Crystallization occurred after a volume of Et_2O equal to the volume of the viscous residue was added to the reactor. Filtration and washing (cold Et_2O) gave 37.6 g (91%) of a white solid: mp 67.5–68.5°; nmr spectrum ($CHCl_3$), τ 3.06 (doublet, 2 H, *J* = 10 cps, ArH), 6.15 (singlet, 6 H, CH_3), 6.61 (multiplet, 8 H, CH_2). *Anal.* ($C_{12}H_{18}BrNO_4$) C, H.

2-Bromo-4,5-dimethoxy-N,N′-bischloroethylaniline (III).—A solution of II (25.6 g, 0.08 mole) in 200 ml of $CHCl_3$ was slowly added to 27 g (0.18 mole) of refluxing $POCl_3$. Refluxing was continued until evolution of HCl ceased. The dark reaction mixture was poured into ice water and extracted with two 200-ml portions of H_2O, dried ($CaCl_2$), and percolated through 80 g of acid-washed alumina (activity I). Passing this solution through silica gel gave III, 25.3 g (89%), as a straw-colored oil: nmr spectrum (CCl_4), τ 3.12 (doublet, 2 H, *J* = 10 cps, ArH), 6.22 (singlet 6 H, CH_3), 6.58 (singlet, 8 H, CH_2). *Anal.* ($C_{12}H_{16}BrCl_2NO_2$) H, N; C: calcd, 40.45; found 39.83.

1-Phenyl-4-(2-bromo-4,5-dimethoxyphenyl)piperazine (IV).—A solution of 10.9 g (0.03 mole) of III and 8.55 g (0.09 mole) of $C_6H_5NH_2$ in 900 ml of 50% Me_2CO–H_2O was refluxed overnight.

(15) W. M. Whaley and C. White, *J. Org. Chem.*, **18**, 184 (1953).

After boiling off the acetone, 500 ml of ice water was added and the solution was saturated with NaCl. The reaction mixture was extracted (Et_2O) and the extract was dried (Na_2CO_3). Stripping off the ether left a brown viscous residue. Trituration of the residue with MeOH yielded 4.2 g (31%) of IV, mp 121.5–122.5° (MeOH).

The N-phenylpiperazines listed in Table I were synthesized by analogous procedures.

1-(2-Bromo-4,5-dimethoxyphenyl)-4-(2-methyl-4,5-dimethoxyphenyl)piperazine.—A solution of 31 g (0.05 mole) of II ditosylate and 25 g (0.15 mole) 4-methyl-5-aminoveratrole in 1 l. of 50% Me_2CO–H_2O was refluxed for 2 days. A solid which precipitated during the course of the reaction was filtered. After washing (Et_2O) and recrystallization (*i*-PrOH), it gave 4.2 g of white glistening flakes.

1-(2-Bromo-4,5-dimethoxyphenyl)-4-tetramethylenepiperazinium Chloride.—A solution of III (14 g) and 20 ml of pyrrolidine in 150 ml of THF was refluxed for 2 days. Filtration of the cooled reaction mixture gave 16 g of a tan solid. Extraction with hot *i*-PrOH left the piperazinium salt as a white solid (8.9 g).

The piperazinium salts listed in Table II were prepared in a like manner.

Preparation of Some Sulfonamide and Diaminodiphenyl Sulfone Analogs of 1,4-Naphthoquinone[1]

F. I. CARROLL, KENNETH H. DUDLEY, AND H. WAYNE MILLER

Chemistry and Life Sciences Laboratory, Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received May 22, 1968

Although the activity of sulfonamide drugs against human malaria has been disappointing, the capacity of these drugs to potentiate the activity of other antimalarial agents has renewed an interest in this class of compounds.[2,3] Zbinden has pointed out the striking differences in the lipid solubility and pK_a of various sulfonamides and the consequent influences of these differences on the kinetics of drug absorption and excretion.[4] We have prepared a series of sulfonamides which incorporate a naphthoquinone residue at the N^4 nitrogen[5] for evaluation of antimalarial activity.[6] The naphthoquinone analogs reported herein were prepared from a series of sulfonamides which show a spectrum of variances in their physical dispositions.[4]

Table I summarizes the synthesis of the sulfonamide and diaminodiphenyl sulfone analogs of 1,4-naphthoquinone. N^4-(1,4-Naphthoquinonyl)sulfanilamide (Ia) and N-(1,4-naphthoquinonyl)-α-amino-*p*-toluenesulfonamide (Ib) were prepared by the condensation of the appropriate sulfonamide with 2-hydroxy-1,4-naphthoquinone in 80% AcOH (procedure A, Table I). Calandra and Adams reported that the treatment of 2,3-dichloro-1,4-naphthoquinone with sulfadiazine in refluxing ethanol catalyzed by N,N-diethylaniline gave N^4-(3-chloro-1,4-naphthoquinonyl)sulfadiazine (Ic).[7] Attempts to repeat this preparation were unsuccessful. Tlc[8] showed very faint orange spots that could be attributed to the expected product, but the yield was so small that isolation was impossible. The reaction of 2,3-dichloro-1,4-naphthoquinone with sulfadiazine in DMF catalyzed by K_2CO_3 (procedure C, Table I) also gave only trace amounts of the desired product. The N^4-(3-chloro-1,4-naphthoquinonyl)sulfadiazine (Id) could be obtained, however, by treating 2,3-dichloro-1,4-naphthoquinone with sulfadiazine in DMSO catalyzed by K_2CO_3 (procedure B, Table I). The product obtained had mp 298–300° compared to mp 256° reported by Calandra and Adams. However, the analysis and ir spectra are in agreement with the assigned structure. The naphthoquinone sulfonamides Id and Ie could be obtained by procedures D, C, or B, but again procedure B was the method of choice. The analogs If–j were prepared in satisfactory yield by the procedure of Calandra and Adams (procedure D, Table I). The 3-chloronaphthoquinonyl derivative Ii of diaminodiphenyl sulfone (DDS) is the product of the reaction using 1:3 and 3:1 ratios, respectively, of 2,3-dichloro-1,4-naphthoquinone and DDS. The identity of the product from these reactions was established by mixture melting point, tlc, and comparison of ir spectra. The analytical data were in agreement with the formula $C_{22}H_{15}ClN_2O_4S$, and the compound gave a mono-N-formyl (Ik) and mono-N-acetyl (Il) derivative. The DDS derivatives were of interest since many chloroquine-resistant strains of malaria parasites did not show cross resistance to DDS.[9]

The sulfonamide and DDS analogs of 1,4-naphthoquinone, have been tested against *Plasmodium berghei* in mice by Dr. Leo Rane.[10,11] These compounds exhibited negligible antimalarial activity. N^4-(3-Chloro-1,4-naphthoquinonyl)sulfadiazine (Ic) which showed a 2.3-day extension of survival time at a dose of 80 mg/kg and a 2.9-day extension at 320 mg/kg was the most active compound.[12] Deaths occurring on days 2–5 after infection are attributed to drug action and counted as "toxic" deaths. Control animals do not die before day 6. According to this criterion, these compounds were not toxic at a dose of 640 mg/kg.

(1) This investigation was carried out under Contract No. DA-49-193-MD-2862 with the Department of the Army and the U. S. Army Research and Development Command. This paper is Contribution No. 390 from the Army Research Program on Malaria.

(2) (a) D. C. Martin and J. D. Arnold, *J. Am. Med. Assoc.*, **203**, 476 (1968); (b) P. J. Bartelloni, T. W. Sheehy, and W. D. Tigertt, *ibid.*, **199**, 173 (1967).

(3) Using a combination of 2-sulfanilamido-3-methoxypyrazine (Sulfalene) and 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (trimethoprim), Martin and Arnold[2] effected radical cures against a normal, as well as a chloroquine–quinine–pyrimethamine-resistant *Plasmodium falciparum*.

(4) G. Zbinden, "Molecular Modifications in Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 25.

(5) In a uniform nomenclature of sulfonamide drugs, the sulfonamide nitrogen is designated N^1 and the aromatic amino nitrogen N^4.

(6) Molecular modification by N^4 acetylation, alkylation, arylation, or arylsulfonylation renders the sulfonamide drugs, as a class, inactive. Two exceptions to this N^4 substitution generalization are N^4-phthalylsulfathiozole and N^4-succinylsulfathiozole.[4] In addition Calandra and Adams[7] found that the incorporation of the 2-(3-chloro-1,4-naphthoquinonyl) group at the N^4 position of certain sulfanilamides gave analogs which were active inhibitors of acid production by bacteria in the oral cavity. Fieser and colleagues have shown that certain 1,4-naphthoquinones have considerable antimalarial activity; see L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Larenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967), for a review of this work.

(7) J. C. Calandra and E. C. Adams, Jr., *J. Am. Chem. Soc.*, **72**, 4804 (1950).

(8) Tlc on 25 × 75 mm microscope slides covered with Brinkmann silica gel HF, eluent C_6H_6–EtOH–AcOH (9:1:1).

(9) A. B. G. Laing, *J. Trop. Med. Hyg.*, **63**, 25 (1960).

(10) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(11) Printout interpretation for rodent antimalarial test results, Walter Reed Army Institute of Research.

(12) Antimalaria test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.