Analogs of the Antimalarial 2-Bromo-*N*,*N*-bis(diethylaminoethyl)-4,5-dimethoxyaniline. 2-Position Variations[1,2]

EUGENE L. STOGRYN

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

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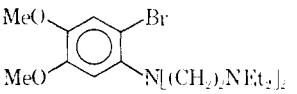
Variations of the antimalarial agent I in which Br was substituted by N, O, S, and C functionality were synthesized for antimalarial testing. Aromatic nucleophilic displacement of halogen from halonitroveratroles followed by reduction of NO_2 yielded 2-position substituted aniline precursors to target structures. Metalation of the anilines prior to reaction with 2-chlorotriethylamine was the most effective method for the bis-N-alkylation of aryl N. With the exception of *N*,*N*-bis(diethylaminoethyl)-4,5-dimethoxy-*o*-phenylenediamine (**2**), no significant activity against *Plasmodium gallinaceum* was observed.

The degree of antimalarial activity of aminopyrocatechol dialkyl ether[3,4] derivatives periodically rekindles interest in these materials. The most efficacious member of the class described to date is 2-bromo-*N*,*N*-bis(diethylaminoethyl)-4,5-dimethoxyaniline (I), which has been suggested[5] to be of value as a prophylactic or radical curative antimalarial agent.



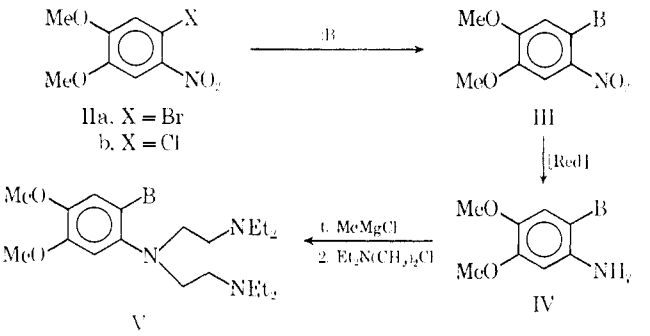
I

The relationship between the structure of the alkoxy and amino functions of aminopyrocatechol derivatives such as I and antimalarial activity was clearly defined by the studies of Schoenhofer.[4] Recently,[6] some of these earlier findings have been confirmed in other antimalarial activity screens. Structure-activity studies with regard to functionality in the ring 2 position have not been described. One might anticipate that substituents in this position would exert quite a dramatic effect on activity because of possible mesomeric and steric influences on the triamine side chain. Such influences may be reflected in the pronounced decrease in antimalarial activity observed when the 2-Br of I is replaced by H.[7]

Chemistry.—The reported[5,8] synthesis of I involves the bis-N-alkylation of 3,4-dimethoxyaniline with 2-chlorotriethylamine. Bromination of this product in AcOH places Br in the 2 position of the aromatic ring. It is apparent that this approach imposes synthetic limitations on the variation of the 2 position.

The new synthetic route we developed to prepare 2-position variations of I is shown in Scheme I.

SCHEME I



Both IIa and IIb were obtained in good overall yield by the halogenation and nitration of veratrole.[10] Replacement of halide from II, by nucleophiles, was conducted in hot EtOH solutions either at atm pressure or in an autoclave at autogenous pressures. Introduction of N and O functionality was best effected by the $Sn_{Ar}1$[11] replacement of Cl^-. Considerably poorer yields resulted when the leaving group was Br^-. In contrast to this, displacement of Br^- by RS^- was the most effective way to place S functionality in the 2 position. These results appear to be in accord with published rates of displacement as related to the nature of the leaving group and the nucleophile.[12]

Reduction of the NO_2 group of III to the primary amine was conveniently accomplished with N_2H_4–Ra Ni[6,13] or Sn–HCl. The type III and IV structures prepared for this investigation are listed in Table III.

Two methods were utilized for step IV → V, with method B consistently giving the best results. Alkylation of the primary amines with 2-chlorotriethylamine (method A), gave low yields of bis-N-alkylated products with mono-N-alkylated materials predominating, and in some instances being the exclusive products. In method B, the N-alkylation step was preceded by metallation of the primary arylamine with 2 moles of MeMgCl. This prior metallation technique permitted bis-N-alkylation at relatively low reaction temperatures (refluxing THF). Structural variations of the ring 2 position, synthesized according to Scheme I, are shown in Table I.

(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. 666 from the Army Research Program on Malaria.

(2) For Part II of this series see E. L. Stogryn, *J. Med. Chem.*, **13**, 864.

(3) W. Schulemann and W. Kropp, U. S. Patent 1,757,394 (1930); *Chem. Abstr.*, **24**, 3327(1930).

(4) F. Schoenhofer, "Chemotherapy," Office Tech. Services Rept., P.B.-85033, 1948; FIAT, *Rev. Ger. Sci.*, 43 (1948).

(5) L. H. Schmidt, R. N. Rossau, R. Fradkin, J. Woods, W. Schulemann, and L. Kratz, *Bull. W. H. O.*, **34**, 783 (1966).

(6) E. L. Stogryn, *J. Med. Chem.*, **12**, 185 (1969), and unpublished work.

(7) Against *P. gallinaceum* infected chicks I was curative at the 80 mg/kg level. Dimeplasmin (VI) at the 240 mg/kg level only increased survival time by 1.5 days.

(8) L. M. Werbel, E. F. Elslager, M. P. Hoch, and J. M. Vanderkelen, *J. Pharm. Sci.*, **56**, 1335 (1967).

(9) Farbenfabriken Bayer A. G., Netherlands Application 6,612,827 (1967); *Chem. Abstr.*, **68**, 4760 (1968).

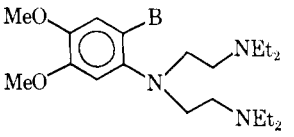
(10) (a) W. M. Whaley and C. White, *J. Org. Chem.*, **18**, 184 (1956); (b) C. A. Fetscher and M. T. Bogert, *ibid.*, **4**, 716 (1939).

(11) J. F. Bunnet, *Quart. Rev.*, **12**, 1 (1958); S. D. Ross in S. G. Cohen, A. Streitweiser, and R. W. Taft, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

(12) A. J. Parker, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Pergamon Press, New York, N. Y., 1963, p 103.

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

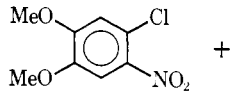
TABLE I



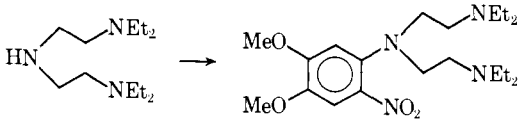
No.	B	Method[a]	Yield, %	Bp °C (mm)	Formula	Analysis[d]
1	NO_2		40	195–197 (0.05)	$C_{20}H_{36}N_4O_4$	C, H, N
2	NH_2		75	180–190 (0.05)	$C_{20}H_{38}N_4O_2$	H, N; C[e]
3	NHCHO		95	194–197 (0.05)	$C_{21}H_{38}N_4O_3$	C, H
4	NMe_2	B	41	155–161 (0.05)	$C_{22}H_{42}N_4O_2$	C, H, N
5		B	55	170 (0.01)	$C_{24}H_{44}N_4O_2$	C, H, N
6		A	18	165–170[b]	$C_{25}H_{49}Cl_3N_4O_2$	C, H
7		B	52	192–194 (0.05)	$C_{26}H_{48}N_4O_2$	C, H, N
8		A	14	175–176 (0.05)	$C_{24}H_{44}N_4O_3$	C, H, N
9		A	15	188–191 (0.05)	$C_{25}H_{47}N_5O_2$	C, H
10	OCH_3	A	20	140–144 (0.001)	$C_{21}H_{39}N_3O_3$	H, N; C[f]
11	OC_6H_5	B	30	>250 (0.05)[c]	$C_{26}H_{41}N_3O_3$	C, H, N
12	$OCH_2C_6H_5$	B	28	>200 (0.05)[c]	$C_{27}H_{43}N_3O_3$	[g]
13	SCH_3	A	10	175–184 (0.01)	$C_{21}H_{39}N_3O_2S$	C, H
14	SC_6H_5	B	53	200–210 (0.05)	$C_{26}H_{41}N_3O_2S$	C, H, N
15	$SCH_2C_6H_5$	B	79	210–218 (0.01)	$C_{27}H_{43}N_3O_2S$	C, H, N
16	SCN				$C_{21}H_{36}N_4O_2S$	C, H, N, O, S
17	CH_3	A	20	138–140 (0.05)	$C_{21}H_{39}N_3O_2$	H, N; C[h]
18	$CH_2CH{=}CH_2$	B	44	155 (0.02)	$C_{23}H_{41}N_3O_2$	C, H, N

[a] Detailed description of the two methods are presented in the Experimental Section. [b] Melting point of the trihydrochloride. [c] Bath temperature. [d] Where analysis are indicated by symbols of the elements analytical results were obtained for those elements within ±0.4% of the theoretical value. [e] C; calcd, 65.48; found, 64.64. [f] C; calcd, 65.10; found, 65.59. [g] Product decomposed during purification; identification based on pmr and ir analysis. [h] C; calcd, 69.04; found, 67.93.

Structure **1** represents an interesting variation of the general synthetic scheme employed for this study. In this modification the triamino side chain was attached to the benzene ring, in a single step, *via* the nucleophilic displacement of Cl^- from IIb with 1,1,7,7-tetraethyldiethylenetriamine. This product appears to be



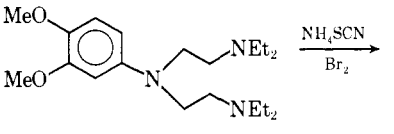
IIb



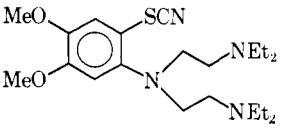
1

the first member of the aminopyrocatechol class of antimalarials having a strong electron-withdrawing group in the position ortho to the triamino side chain. Transformation of NO_2 of **1** into **2** and **3** was accomplished by standard synthetic techniques.

The chemical reactivity of the thiocyanato group precludes the synthesis of **16** by Scheme I. Its preparation was achieved *via* the thiocyanogenation of VI.[4,8] Attempts to purify reaction mixtures consisting of VI and **16** were unsuccessful by either distillation or chromatographic procedures. However, **16** could be obtained free of VI by repetitive thiocyanogenation until the nmr spectra exhibited signals in the aromatic region due only to para protons.



VI



16

Compounds with varying 2-C substituents were also prepared for this study and are listed in Table I. The intermediates for these compounds were obtained *via* the nitration of 4-Me and 4-allylveratrole followed by N_2H_4–Ra Ni reduction.

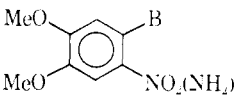
Biological Data.—The target compounds listed in Table I (with the exception of **12**) were screened for antimalarial activity in chicks infected with *Plasmodium gallinaceum* and in the *Aedes aegypti* mosquito carrying *P. gallinaceum*. The results are summarized in Table II. Compound **2** increased the mean survival time of the infected chicks sufficiently (8.4 days) to be classified as active. All the other compounds had only a marginal effect on the survival time. With the exception of **6** and **16**, which caused $^2/_5$ toxic deaths, no pronounced obvious toxicity was observed. Compounds **4**–**11** gave considerable response to the mosquito activity screen, particularly toward suppression of oocysts and sporozoites at the 0.1% drug

TABLE II
ANTIMALARIAL ACTIVITY[a]

No.	Chick: mg/kg	Chick: Δ S.T.[b]	Chick: Toxicity[c]	Toxicity, %	Mosquito[d]: Abnormal oocysts, %	Mosquito[d]: Suppression, % Oocysts	Mosquito[d]: Suppression, % Sporozoites
1	240	0.2	0	100			
2	320	8.4	0				
3	160	0.8	0				
4	320	0.3	0	40	0	100	100
5	320	0.6	0	51	50	50	100
6	320	0.6	2	86	0	100	100
7	320	0.6	0	86	50	50	75
8	320	0.6	0	57	0	100	100
9	320	0.3	0	37	100	0	100
10	120	0.5	0				
11	160	0.8	0	29	0	100	100
13	320	0.6	0	23	0	0	0
14	320	0.6	0				
15	120	0.5	0	77	0	25	0
16	320	0.8	2				
17	120	0.2	0				
18				100			

[a] The avian activity screen was performed by Dr. L. Rane of the University of Miami. The mosquito activity screen was performed by Dr. E. Gerberg. The significance of this screen is described in E. Gerberg, L. T. Richard, and J. T. Poole, *Mosquito News*, **26**, 359 (1966). [b] Δ S.T. refers to the change in mean survival time between control and drug treated chicks. [c] Number of deaths/5 test chicks. [d] Drug concentration, 0.1%.

TABLE III



B	Nitro: Yield, %	Nitro: Mp, °C	Nitro: Analysis[a]	Amine[e]: Yield, %	Amine[e]: Mp, °C	Amine[e]: Analysis[a]
NMe_2	29	129	*b*	76	73	
$N(CH_2)_4$	57	138–140	C, H	85	84	C, H, N
$N(CH_2)_5$	88	82–83	C, H, N	74	52	C, N
$N(CH_2)_6$	32	54–55	C, H	80	202[k]	H, N; C[m]
$NCH_2CH_2OCH_2CH_2$	67	115–117	H; C[c]	90	109	C, H, N
$NCH_2CH_2NCH_2CH_2$ (Me)	70	112–113	H, N; C[d]	82	97	H; C[p]
OCH_3		130	*b*	42	92–93	*q*
OC_6H_5	19	100–101.5	C, H, N	96	*l*	C, H, N
$OCH_2C_6H_5$[i]	75	140–142	C, H, N	38	72	C, H
SCH_3[j]	95	136–137	C, H, N	90	67–68	H; C[r]
SC_6H_5[j]	95	115–117	H, N, S; C[e]	87	167–170[m]	C, H, N, S
$SCH_2C_6H_5$[j]	98	178–179	H, S; C[f]	83	88–89	C, H, N, S
CH_3		118–119	*g*		109	*q*
$CH_2CH{=}CH_2$		38–39	*h*	63	*n*	C, H, N

[a] See footnote *d*, Table I. [b] A. H. Parijs, *Chem. Abstr.*, **23**, 4204[9] (1929). [c] Calcd, 53.72; found, 54.40. [d] Calcd, 55.52; found, 54.67. [e] Calcd, 57.72; found, 57.09. [f] Calcd, 58.98; found, 59.58. [g] P. Rayet, M. Prost, and M. Urbain, *Helv. Chim. Acta*, **39**, 87 (1956). [h] G. R. Clemo and J. H. Turnbull, *J. Chem. Soc.*, 1870 (1949). [i] Reduction of the NO_2 group was achieved with N_2H_4–Ra Ni according to ref 6. [j] Reduction was accomplished with Sn–HCl according to the described procedure. [k] Melting point of HCl salt. [l] Product distilled at 180° (bath temp) (0.05 mm). [m] Melting point of HCl salt. [n] Boiling point 117–120° (0.1 mm). [o] Calcd, 58.74; found, 57.99. [p] Calcd, 62.12; found, 62.97. [q] *Chem. Abstr.*, 1, 311[7] (1907). [r] Calcd, 54.24; found, 53.66.

concentration level. However, the next lower level, 0.01%, produced only marginal response. Compounds **1**, **5**, **6**, **10**, **15**, and **17** were also inactive at the maximum dose level (640 mg/kg) in mice infected with *P. berghei*.[14] No clear activity pattern with regard to electronic effects or steric effects are apparent from our studies.

(14) For a detailed discussion of this screen see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

Experimental Section

5-Nitro-4-*N*-substituted-veratroles (Table III).—A steel autoclave containing 0.3 mole of IIb, 1 mole of amine, and 500 ml of anhyd EtOH was heated at 140° overnight. The contents of

the cooled bomb were placed in a rotary evaporator and the solvent removed *in vacuo*. The residue was dissolved in dil HCl and extracted with Et_2O. Neutralization of the aq phase pptd the desired NO_2 derivatives as yellow to bright red solids.

4-Benzyloxy-5-nitroveratrole.—A mixture of 11.9 g of 4,5-dimethoxy-2-nitrophenol,[15] 11.3 g of $PhCH_2Br$, and 8.3 g of K_2CO_3 in 100 ml of Me_2CO was stirred at reflux temp for 3 days. The cooled reaction mixture was filtered and the filter cake washed with Et_2O. Removal of solvent *in vacuo* and recrystallization from EtOH gave the titled compound as yellow needles.

5-Nitro-4-phenoxyveratrole.—The procedure reported for the synthesis of *p*-nitrodiphenyl ether[16] was used to prepare the titled compound. Thus, 43.4 g of IIb, 32 g of PhOH, 16 g of KOH, and 0.5 g of Cu catalyst gave the product as a light yellow solid.

5-Nitro-4-*S*-substituted-veratroles (Table III).—The 5-NO_2-4-*S*-substituted-veratroles were prepared by refluxing NaSR in MeOH (preparing *in situ* from 25% $NaOCH_3$ in MeOH) and IIa for 6 hr. The cooled reaction mixtures were filtered and washed with H_2O. Recrystallization from EtOH gave the NO_2 compounds listed in Table III.

2-*S*-Substituted-4,5-dimethoxyanilines (Table III).—The following procedure typifies the reduction of type III structures containing S functionality. To a hot slurry of 30.6 g of 4-methylthio-5-nitroveratrole and 49 g of Sn in 500 ml of EtOH was slowly added 205 ml of concd HCl. During the addition, the solids gradually dissolved and the color of the solution was discharged. Refluxing and stirring was maintained for 0.5 to 1 hr after addition of acid was complete. The cooled solution was poured into ice, followed by 330 ml of 50% NaOH. The white ppt was filtered, dried, and extracted with hot Et_2O. Removal of Et_2O and recrystallization from hexane gave the amine as a colorless solid.

Bis-N-alkylation of 2-Substituted-4,5-dimethoxyanilines.—Typical examples of the preparative methods used to obtain the target compounds listed in Table I are given. **Method A.**—A solution of 13 g of 2-morpholino-4,5-dimethoxyaniline and 22 g of 2-chlorotriethylamine in 150 ml of DMF was refluxed overnight. After filtration and removal of the DMF under reduced pressure, the residue was treated with dil base, extracted with pentane, and dried (Na_2CO_3). Distillation through a short column gave two main cuts, 170–181° (0.01 mm) (2.9 g) and 181–185° (0.01 mm) (9.8 g). The lower boiling fraction solidified on standing. This fraction was dissolved in a small amount of pentane and cooled to −40°. The solid which pptd (2.5 g, mp 66–68°) was identified as mono-N-alkylated material. Treatment of the higher boiling fraction in the same manner gave an additional small amount of the solid product.

The combined pentane filtrates were distd through a short column, giving 3.6 g of **8**, bp 175–176° (0.05 mm), as a pale yellow viscous oil.

Method B.—To a solution of 2-pyrrolidino-4,5-dimethoxyaniline (0.028 mole), in 100 ml of THF was added 0.06 mole of MeMgCl (1.6 *M* in Et_2O). Freshly distilled 2-chlorotriethylamine (0.13 mole), in 50 ml of THF was added and the reaction mixture refluxed overnight. After removal of solvents under reduced pressure the residue was dissolved in aq NH_4Cl and extracted with pentane. Distillation of the residue gave a 55% yield of **5** as a pale yellow oil, bp 170° (0.01 mm).

***N*,*N*-Bis(diethylaminoethyl)-4,5-dimethoxy-2-nitroaniline (1).**—A mixture of 21.4 g of IIb, 41.4 g of 1,1,7,7-tetraethyldiethylenetriamine and 17.1 g of NaOAc in 100 ml of DMSO was stirred and heated on a steam bath for 24 hr. Pouring the red reaction mixture into 1.5 l. of ice–water containing 8 g of NaOH, caused pptn of 18 g of IIb. Extraction of the filtrate with pentane and distillation through a short-path still gave 3 g of a red oil. Final purification was effected by chromatography through base-treated silica gel[17] (2.5 g isolated from the Et_2NH eluate).

***N*,*N*-Bis(diethylaminoethyl)-4,5-dimethoxy-*o*-phenylenediamine (2).**—To 9.2 g of 1 in 45 ml of hot EtOH containing 8.2 g of Sn was added 35 ml of concd HCl. After the addition of acid was complete, stirring and heating was continued for 1 hr. During this period the solution changed in color from a cherry red to a brown–yellow. The reaction mixture was then poured into ice–water containing 56 ml of 50% NaOH. The ppt was filtered and extracted with 450 ml of warm Et_2O. The aq filtrate was satd with NaCl and extracted with 300 ml of Et_2O. Distillation of the combined extracts gave 6.3 g (75%) of **2** as a yellow–orange oil.

***N*,*N*-Bis(diethylaminoethyl)-4,5-dimethoxy-*N'*-formyl-*o*-phenylenediamine (3).**—Formic acid (5 g) and 4 g of **2** were refluxed for 4 hr. Distillation through a short-path still gave **3** as a light yellow oil in virtually quantitative yield.

***N*,*N*-Bis(diethylaminoethyl)-4,5-dimethoxy-2-thiocyanatoaniline (16).**—Thiocyanation of VI was effected by the procedure used to thiocyanate dimethylaniline.[18] Thus, 0.06 mole of VI and 0.126 mole of NH_4SCN in 75 ml of AcOH when treated with 0.06 mole of Br_2 yielded 21 g of a dark-colored oil containing about 75% (based on pmr) of **16**. This mixture of product and VI was dissolved in AcOH and treated as above with 0.063 mole of Br_2. The product was dissolved in hot pentane and treated with charcoal. Solvent removal on a rotary evaporator yielded a reddish viscous oil which, by pmr, was free of VI.

(15) R. Quelet, *Bull. Soc. Chim., Fr.*, 349 (1959).

(16) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol II, Wiley, New York, N. Y., 1943, p. 445.

(17) Base-treated silica gel was prepared by mixing 1 kg of silica gel (100–200) mesh) with a solution of 30 g NaOH in 300 ml of H_2O and 300 ml of MeOH. The treated gel was then washed twice with MeOH, air dried, and then dried at 750°F.

(18) R. Q. Brewster and W. Schroeder, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 574.