any acid by-product.[21] The $CHCl_3$ solution was dried ($NaSO_4$), charcoaled, and evaporated.

(2) The 8-quinolinemethanol (17.3 mmoles), Et_3N (17.5 g, 170 mmoles), and 30 ml of dry DMSO were mixed and heated to 70°. Pyridine–SO_3 (13 g, 83 mmoles) in 30 ml of DMSO was added slowly while stirring. The mixture was stirred at 70° for 2 hr. It was poured into H_2O, stirred for 15 min, and filtered. The precipitate was washed with H_2O.

8-(1,2-Epoxyethyl)quinolines (Oxiranes).—Henry's procedure[22] of addition of aldehyde to a four- to fivefold excess of dimethylsulfonium methylide gave unsatisfactory yields of impure products. The following procedure was uniformly successful.

Dimethylsulfonium methylide was prepared by Corey's method.[7] The stoichiometric amount of this ylid, immediately after preparation, was forced by N_2 into a solution of the 8-quinolinecarboxaldehyde in THF, and the mixture was stirred at room temperature for 1 hr. The THF was removed under reduced pressure at 50° and the remaining solution was diluted with H_2O. The precipitated oxirane was filtered and washed with H_2O.

α-(Dialkylaminomethyl)-8-quinolinemethanols.—The 8-quinolinemethanols listed in Table III were all prepared by the direct condensation of the corresponding oxirane with the appropriate secondary amine, using 4–5 moles of amine/mole of oxirane. The excess of amine was removed either by distilling under reduced pressure or by fractional pptn of the HCl salt. The Et_2O solution of amino alcohol was charcoaled and the amino alcohol was pptd as the HCl salt.

Acknowledgments.—Nmr spectra were provided to us through the courtesy of Dr. William J. Welstead, Jr., A. H. Robins Company, Inc., Richmond, Va. Microanalysis were performed by Microanalysis, Inc., Wilmington, Del.

(21) The 2-(4-chlorophenyl)-8-methylquinolines gave good yields of the aldehydes with no formation of the corresponding carboxylic acids, but the 2-unsubstituted compounds readily overoxidized.

(22) W. G. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *J. Med. Chem.*, **11**, 1221 (1968).

New Synthesis of Antimalarials Related to 2-Bromo-4,5-dimethoxy-*N*,*N*-bis(diethylaminoethyl)aniline. Terminal Nitrogen Modifications[1,2]

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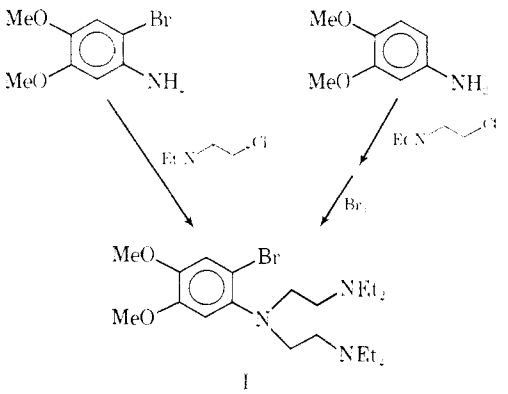
The antimalarial I can be synthesized in one step by a novel N-alkylation technique. The metalation of 2-bromo-4,5-dimethoxyaniline and subsequent reaction with various N mustards yielded modifications of I with the triamine terminating in small and medium sized rings. None of the reported modifications showed significant antimalarial activity.

The response of malaria-infected canaries[3] and Rhesus monkeys[4] toward treatment with I revived interest in a rather old class of antimalarials.[5] Anticipating that I in combination with an effective schizonticide might be of value in combating drug-resistant strains of *Plasmodium falciparum* structural variations of the basic side chain were synthesized for evaluation in antimalarial screens.

A basic side chain comprised of one or more amino nitrogens is a common structural feature of many classes of antimalarial drugs. It has been suggested that the distribution and absorption of a drug in the host is controlled by this ubiquitous basic side chain.[6a,b] As might be anticipated the requisite structural features of this side chain are quite specific. To illustrate, activity in the amino pyrocatechol dialkyl ether[7] antimalarials has only been observed when the triamine conforms to the structure shown in I. Russell[8] has described the structure of the basic side chain characteristic of other anitmalarials.

The structural limitations imposed on the two terminal nitrogens has received little attention. We have synthesized variations of I in which the basic side chain is terminated in small and medium sized rings. It seemed desirable to evaluate the influence on activity imposed by the rotational and conformational variations of this type of side chain termination.

Chemistry.—From the standpoint of simplicity and potential versatility the synthesis of I by the direct alkylation of 2-bromo-4,5-dimethoxyaniline would be desirable. This approach to I has been examined by us



I

as well as others,[9] with little success. The difficulty arises from a combination of the rather drastic reaction

(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. 652 from the Army Research Program on Malaria.

(2) For Part I of this series see E. L. Stogryn, *J. Med. Chem.*, **12**, 185 (1969).

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

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

(5) (a) W. Schulemann and W. Kropp, U. S. Patent 1,757,394, May 6, 1930; (b) R. Green, *Lancet*, **217**, 1137 (1929); (c) R. Green, *Bull. Inst. Med. Res. Fed. Malaya*, **28**, 29 (1929); (d) J. A. Sinton, *Indian J. Med. Res.*, **17**, 815 (1930).

(6) (a) O. Yu. Magidson, N. M. Delektorskaya, and I. M. Lipovich, *Arch. Pharm.*, **272**, 74 (1934); (b) O. Yu. Magidson and A. M. Grigorovskii, *Ber.*, **69B**, 396 (1936).

(7) F. Schoenhofer, "Chemotherapy," Office of Technical Services Report, P.B.-85033, 1948; FIAT, Review of German Science, 43.

(8) P. B. Russell in "Medicinal Chemistry," A. Burger, Ed., Interscience, New York, N. Y., 1960, p 814.

(9) L. M. Werbel, E. F. Elslager, M. P. Hutt, and J. M. Vanderbelt, *J. Pharm. Sci.*, **56**, 1335 (1967).

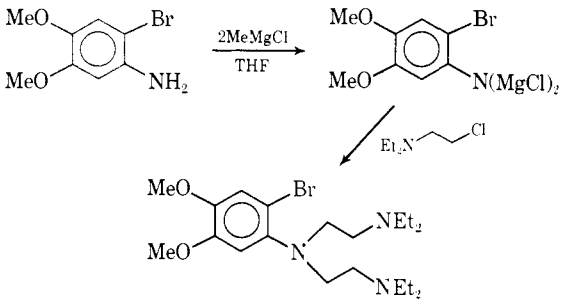
conditions required to effect bis-N alkylation of arylamines[10] and the thermal lability of 2-bromo-4,5-dimethoxyaniline.[11] These problems are circumvented when I is synthesized by the bis-N alkylation of 3,4-dimethoxyaniline followed by bromination.[9,12] However, this latter technique imposes restrictions on the type of modifications that can be prepared.

We have developed a synthesis of I starting from 2-bromo-4,5-dimethoxyaniline which requires only mild reaction conditions and appears to have general applicability.

It is reasonable to assume that bis-N alkylation of arylamines is rather difficult because of the relatively low order of nucleophilicity of the aromatic nitrogen. Conversion of the neutral amine into the negatively charged amide ion, by proton removal, should lower the energy requirements for N alkylation. Broser[13] has recently demonstrated this point by the facile bis-N silylation of *N*-lithio-*o*-haloanilines. In our laboratory the lithiation of 2-bromo-4,5-dimethoxyaniline with 2 moles of BuLi followed by reaction with 2-chlorotriethylamine yielded I. However, this was accompanied by substantial quantities of the desbromo variation of I [3,4-dimethoxy-*N*,*N*-bis(diethylaminoethyl)aniline]. The formation of the latter product is explicable in terms of a halogen–metal interchange[14] between BuLi and the bromoaniline.

In view of the rarely reported halogen–metal interchange reaction between Grignard reagents and aryl halides the removal of protons from the arylamine by this base presented itself as an attractive alternative to the use of BuLi. Using the methyl Grignard as the proton abstractor, I was obtained in 71% yield according to Scheme I. Separation of bis- and mono-N alkylated

SCHEME I



products could be conveniently accomplished by distillation or chromatography through a base-treated silica gel column. The bis-N alkylated product was eluted from the column with Et_2NH.

Tlc (silica gel) of the crude reaction mixture gave only a faint spot on the tlc plate corresponding to mono-N-alkylated material. The clean ^1H nmr signals, doublet centered at τ 3.16 ($\sqrt{AB}$ = 11 Hz), clearly established that bromine had not been lost during the reaction sequence.

(10) The difficulty in N alkylation of arylamines with alkylaminoalkyl halides is described by M. Carmack, L. W. Kissinger, and I. Von. [*J. Amer. Chem. Soc.*, **68**, 1551 (1946)] and W. M. Lauer, C. Rondestvedt, R. T. Arnold, N. L. Drake, J. V. Hook and J. Tinker [*ibid.*, **68**, 1546 (1946)].

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

(12) Farbenfabriken Bayer A.G., Netherlands Application 6,612,827 (3/17/67); *Chem. Abstr.*, **68**, 4760 (1968).

(13) W. Broser and W. Harrer, *Angew. Chem.*, **77**, 1139 (1965).

(14) R. G. Jones and H. Gilman, Org. React., **6**, 339 (1951).

The N mustards employed in the synthetic aspects of our structure–activity studies are listed in Table I.

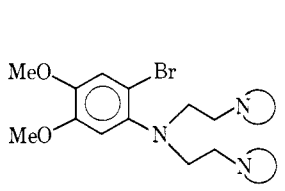
TABLE I

R	—R—OH Yield, %	—R—OH Bp, °C (mm)	—R—Cl Yield, %	—R—Cl Bp, °C (mm)	Ref
$(CH_2)_4$—N—	78	89–92 (23)	95	58 (10)	*b*
$(CH_2)_5$—N—	85	94–96 (23)	81	36 (2)	*c*
$(CH_2)_6$—N—	75	114–115 (23)	75	39 (2)	*d*
$(CH_2)_6$—N(CH_2—	44	115–120 (9)	75	100 (7)	*f*, *g*
$CH_2CH_2OCH_2CH_2$—N—	75	118–120 (23)	54	57 (2)	*e*
$(CH_2)_4$—CHNMe	42	116–117 (17)	58	86–88[a]	*f*, *h*
$(CH_2)_5$—CHNMe	76	129–133 (17)	33	106 (10)	*e*
$(CH_2)_7$—CHNMe	47	163–168 (17)	56	166–167[a]	*f*, *i*
PhNMe	93	162–167 (15)	60	125–130 (2)	*e*

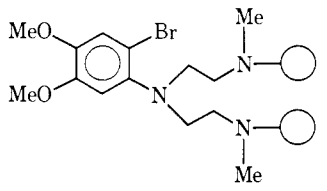
[a] Melting point of hydrochlorides. [b] J. B. Wright, H. G. Kollof, and J. H. Hunter, *J. Amer. Chem. Soc.*, **70**, 3098 (1948). [c] F. F. Blicke and C. E. Maxwell, *ibid.*, **64**, 428 (1942). [d] S. L. Shapiro, T. Bazga, K. Weinberg, and L. Freedman, *ibid.*, **80**, 3726 (1958). [e] G. Gabel, *Bull. Soc. Chim. Fr.*, **41**, 936 (1927). [f] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theoretical value. [g] Calcd for $C_9H_{18}ClN$: C, H. [h] Calcd for $C_8H_{17}Cl_2N$: C, H, N. [i] Calcd for $C_{11}H_{23}Cl_2N$: C, H, N.

Several of these have been described in the literature. In our study the amino alcohols were obtained most conveniently by the reaction of the amine with ethylene oxide in a pressure bottle at 70°. Reaction of the amino alcohols with $SOCl_2$ gave the desired N mustards as the hydrochlorides.

The reaction of the chloroethylamines listed in Table I with 2-bromo-4,5-dimethoxyaniline was conducted according to Scheme I. Structures of type II



II



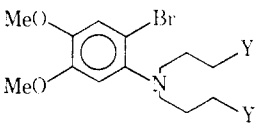
III

were obtained in modest yields. In all cases the N alkylation reaction yielded a mixture of mono- and bisalkylated products. The separation of the monoalkylated from the dialkylated products was readily accomplished by chromatography through base-treated silica gel. The one exception in this series was noted with 1-(2-chloroethyl)morpholine. In the usually employed reaction medium (THF) only a trace of monoalkylated product was isolated. No bisalkylated product was detected. Changing the solvent to Diglyme and heating the reaction to 110° for 3 days only increased the yield of monoalkylated material, again no type II product was found.

The N mustards having exocyclic N, in general, bisalkylated 2-bromo-4,5-dimethoxyaniline more effectively, yielding type III structures. The one exception to this was with *N*-(2-chloroethyl)-*N*-methylaniline. This N mustard failed to yield either mono- or bisalkylated material.

The products of type II and III listed in Table II were obtained as high boiling point viscous liquids which rapidly darkened on exposure to light and air.

TABLE II



Y	Bp, °C (0.05 mm)	Yield, %	Formula	Analysis[a]
$CH_3(CH_2)_3N$	185–195	12	$C_{29}H_{51}N_3BrO_2$	H, N[g]
$CH_3(CH_2)_4N$	>200	37	$C_{32}H_{56}N_3BrO_2$	C, H, N
$CH_3(CH_2)_5N$	>200	29	$C_{34}H_{60}N_3BrO_2$	H[h]
$CH_3(CH_2)_5NCH_2$[c,e]	215	14	$C_{25}H_{43}N_3O_2$	C, H, N
$CH_2CH_2O(CH_2)_2N$[c]	108–109[b]		$C_{24}H_{31}N_2BrO_3$	C, H, N
$CH_3(CH_2)_3CHNMe$	[d]	56	$C_{34}H_{56}N_3BrO_2$	C, H, N
$CH_3(CH_2)_4CHNMe$	245–250	33	$C_{26}H_{44}N_3BrO_2$	C, H, N
$CH_3(CH_2)_5CHNMe$	[d]	80	$C_{36}H_{52}N_3BrO_2$	H, N[i]

[a] This derivative did not bear bromine in the 2 position. [b] Melting point of monoalkylated derivative—no bisalkylated material could be detected. [c] Decomposed on distillation. Purified by column chromatography. [d] Distillation not attempted. Purified by column chromatography. [e] Reaction solvent, Diglyme, temp 110°, time, 3 days. [f] See footnote *f*, Table I. [g] C: calcd, 56.32; found, 56.88. [h] C: calcd, 59.73; found, 60.45. N: calcd, 8.71; found, 8.04. [i] C: calcd, 63.58; found, 64.09.

Biological Data.[15–17]—The structures listed in Table II were screened for antimalarial activity against *P. gallinaceum* infected chicks, the *Aedes aegypti* mosquito carrying *P. gallinaceum*, and *P. berghei* infected mice. Compound I is curative, without toxic deaths, in the bird screen at the 80 mg/kg level. None of the structures listed in Table II significantly improved the mean survival time of infected chicks, even at dose levels as high as 320 mg/kg. Neither the lead structure, I, nor the variations reported herein sufficiently influenced the survival time of test animals in the mosquito and rodent screens to be classified as active.

In light of the electronic and steric similarities between I and the structural variations listed in Table II, the difference in biological response to *P. gallinaceum* was somewhat surprising. However, it should be noted that this is not an unknown phenomenon in biologically active compounds containing basic side chains.

(15) Activity screens were carried out by Dr. Leo Rane of the University of Miami. The test results were made available by Dr. David P. Jacobus of The Walter Reed Army Institute of Research.

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

(17) E. J. Gerberg, L. T. Richard, and J. T. Poole, *Mosquito News*, **26**, 359 (1966).

Experimental Section

2-Bromo-4,5-dimethoxy-*N,N'*-bis(diethylaminoethyl)aniline.—To a solution of 23.2 g (0.1 mole) of 2-bromo-4,5-dimethoxyaniline[2] in 200 ml of dry THF was added 0.22 mole (138 ml of 1.6 *M*) of MeMgCl at ambient temp. After addition was complete, the solution was allowed to stir at room temp for a short period. Freshly distd 2-chlorotriethylamine (31 g, 0.23 mole), was added and the mixture refluxed overnight. By standard work-up procedures a dark-colored oil was isolated. Extraction of this oil with pentane and solvent removal gave 27.5 g (71%) of crude I. A silica gel tlc plate (eluted with THF) indicated only a small amount of monoalkylated material was present. Distillation yielded the product as a pale yellow oil, bp 180–182° (0.05 mm) which darkened on standing.

Chloroethylamines.—The chloroethylamines listed in Table I were prepared according to the following procedure. Pyrrolidine (32 g), ethylene oxide (18 g), and 5 ml of EtOH were charged to a glass pressure reactor and heated overnight at 70°. After removal of volatile material the residue was vacuum distd and the fraction distilling at bp 89–92° (23 mm) was collected.

A solution of 1-pyrrolidinethanol (15 g) in 325 ml of C_6H_6 was added dropwise to 16.9 g of $SOCl_2$ in 490 ml of C_6H_6. After addition was complete the reaction was refluxed for 2 hr. The cooled reaction mixture was filtered and washed several times with Et_2O. The filter cake was dissolved in H_2O, neutralized, and extracted with Et_2O. Distillation gave 1-(2-chloroethyl)-pyrrolidine, bp 58° (10 mm) (95% yield).

1-(3-Chloropropyl)hexahydro-1*H*-azepine.—After the slow addition of 3-bromo-1-propanol (0.3 mole) to 0.6 mole of hexahydro-1*H*-azepine the reaction mixture was heated for 16 hr on a steam bath. The cooled reaction mixture was diluted with Et_2O, filtered, washed with aq Na_2CO_3, and dried. Removal of the Et_2O and vacuum distillation gave hexahydro-1*H*-azepine-1-propanol, bp 115–120° (9 mm). Conversion of the amino alcohol into the title compound was effected with $SOCl_2$ in the manner previously described.