2-Phenyl-4′,6,8-trichloro-4-quinolylethylene oxide, mp 183–185°, was obtained as a gift from the Walter Reed Army Institute of Research. The bromohydrin precursor has been described.[8]

α-(N-Substituted aminomethyl)-2-phenyl-4-quinolinemethanols (Table I).—The oxide (0.01 mole) and the amine (0.011–0.02 mole) were dissolved in 10–20 ml of DMF and the solution was stirred in a closed flask at 100–110° for 10 hr. The solution was diluted (H_2O) to precipitate the crude product; when emulsions formed, they were coagulated by stirring in a little NaCl. The crude product was recrystallized from the solvent specified in Table I. In a few cases the free base was difficult to handle as such and was therefore converted to the hydrochloride salt by alcoholic or ethereal HCl. The lower amine/oxide ratio was used when water insolubility of the amine might complicate work-up of the product. The higher ratio was used in the case of water-soluble amines. In the case of n-Bu_2NH the higher ratio was used and excess amine was removed by steam distillation. In the case of 1-aminoadamantane the free base[14] was prepared from commercially available 1-aminoadamantane hydrochloride.

All of the compounds described in Table I are insoluble in H_2O and most are moderately soluble in alcohol solvents. We found that these compounds caused moderately severe irritation of the skin.

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Some Characteristics of Two Bipiperidyl Mustards[1]

CHARLES C. PRICE, PRASADA RAO KONERU,[2] AND RICHIRO SHIBAKAWA[2]

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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The stability of diethyl-2-chloroethylamine (I) against cyclization at pH 7 suggested that other mustards with pK_a of 7 or higher might be so extensively protonated under biological conditions as to resist cyclization. This led us to reinvestigate a potential cross-linking difunctional mustard which might fit in this category, N,N′-bis(2-chloroethyl)-4,4′-bipiperidyl (II).[3] This compound has been reported earlier as biologically inactive.[3] We have confirmed this inactivity as well as that for the hydroxylethyl analog and N,N,N′,N′-tetramethyl-4,4′-piperidyl (III). The cyclized imonium form of II, however, was found to have a remarkable obesifying effect on mice.[2,4] The analog of II, N,N′-bis(2-chloroethyl)-4,4′-bipiperidylethane also shows this obesifying effect.

Reports by Yamamoto[5] that DNA and RNA bacteriophages are inactivated by conventianal difunctional mustards but not by monofunctional mustards led to a cooperative investigation of the effects of the bipiperidyl mustard. Dr. Yamamoto found II_{im} inactivated double-stranded DNA (P_{22} and T_5), single stranded DNA (S_{13}), and RNA (MS_2) phages, while a monofunctional analog, the imonium form of N-2-chloroethylpiperidine, inactivated neither.[6] These results are further strong support for the alkylating action of II_{im} leading to inter- or intrachain cross-links.

Experimental Section

4,4′-Bipiperidine[7] was converted to the bis-N-hydroxyethyl (VI) and bis-N-chloroethyl (VII) derivatives.[3] From alkaline titration data, the pK_a data in Table I were estimated by the method of Speakman.[8]

TABLE I

ACID DISSOCIATION CONSTANTS OF BIPIPERIDYL COMPOUNDS, 25°

Compd	pK_a
II	9.47, 10.88
$HOCH_2CH_2$	7.93, 9.19
$ClCH_2CH_2$	6.91, 8.09

Cyclization of II to II_{im} was determined by Volhard titration of chloride ion liberated, as summarized in Table II. After 1 hr, 50 ml of the solution of II_{im} was diluted with 50 ml of 0.005 M thiosulfate. The rate of reaction is summarized in Table III.

TABLE II

CYCLIZATION OF II, 0.005 M, pH 9.0, 25° [a]

Time, min	% Cl^-
15	28.5
30	80
45	100

[a] $k_1 = \sim 3.4 \times 10^{-1}$ sec^{-1}.

TABLE III

REACTION OF II_{im} (0.0025 M) WITH THIOSULFATE (0.0025 M), 25°, pH 9[a]

Time, min	% II_{im} reacted
15	31
30	44
60	56
120	65
180	74

[a] $k_{S_2O_3} = \sim 0.1$ l. mole^{-1} sec^{-1}.

N,N′-Bis(2-hydroxylethyl)-4,4′-dipiperidylethane was prepared from 4,4′-dipiperidylethane[7] by treating an EtOH solution with ethylene oxide followed by evaporation and recrystallization from MeOH (45% yield), mp 107–109°. *Anal.* ($C_{16}H_{32}N_2O_2$) C, H, N.

Conversion to **N,N′-bis(2-chloroethyl)-4,4′-dipiperidylethane dihydrochloride** was accomplished by $SOCl_2$ in $CHCl_3$, recrystallization from MeOH gave colorless needles (80%), mp above 310°. *Anal.* ($C_{16}H_{30}Cl_2N_2$) C, H, N, Cl.

N-(2-Chloroethyl)piperidine hydrochloride was prepared from the hydroxyethyl compound, bp 79° (5 mm), $n^{20}D$ 1.4776 (lit.[9] $n^{25}D$ 1.4775), by stirring overnight with $SOCl_2$ in CCl_4. After removal of excess $SOCl_2$ by distillation, filtration, and recrystallization from EtOH, the product melted at 238° (73%). *Anal.* ($C_7H_{15}Cl_2N$) C, H. An earlier sample reported to be this compound, mp 376°,[10] was undoubtedly the piperazinium dimer.

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