reported until the work is complete and bioassay results are available.

Experimental Section[15]

General Procedure. Conversion of Arylaldehydes to Aryloxiranes.[16]—Into a round-bottom flask was introduced 50% NaH–oil dispersion in a molar amount four times that of the aldehyde to be used. Dry N_2 was passed through the flask during this and all subsequent operations. The oil was removed from the NaH by washing three times with pentane, the pentane being removed by pipet after each wash. Residual pentane was removed by evacuating the flask and refilling it with N_2. DMSO, about 12 times the weight of NaH–oil used, was added and the mixture was stirred at 70–75° until H_2 evolution ceased (*ca.* 0.5–0.75 hr). The solution of DMSO anion was stirred and chilled in an ice–salt bath, after adding a volume of THF equal to that of the DMSO. $Me_3S^+ \cdot I^-$ (molar amount equal to that of the NaH) in DMSO (1 g of salt/4–5 ml of DMSO) was added over *ca.* 3 min. The resulting solution of $Me_2S{=}CH_2$ was then treated over 1–2 min with a THF solution of the aldehyde. The cooling bath was removed and, after stirring for 0.5–1 hr, H_2O was added and the oxirane was isolated by extraction (Et_2O). At this point the Et_2O could be removed carefully to leave the oxirane in virtually quantitative yield. Usually, however, di-*n*-heptylamine (3 equiv/equiv of aldehyde) was added to the Et_2O extracts before boiling off the solvent, and the residue was taken directly to the next step of the sequence. In no instance was the oxirane characterized.

General Procedure. Amino Alcohols from Aryloxiranes—A mixture of the oxirane and 3 molar equiv of diheptylamine was heated in an oil bath under N_2 at 145–155° until tlc (silica gel F) indicated essentially complete disappearance of the oxirane (1-4 hr). The excess diheptylamine was removed from the reaction mixture in a sublimation apparatus at 70–150° (1–8 mm) while being stirred to prevent splattering. Where tlc indicated substantially one component, the residue of product, in Et_2O or absolute EtOH solution, was treated with 1 or 2 equiv (depending on the number of basic nitrogens in the molecule) of 18% HCl in EtOH. Slow dilution with additional Et_2O caused precipitation of the amino alcohol salts in pure condition. When tlc indicated that significant by-products were present, preliminary purification was effected by chromatography over alumina, using 30–60° petroleum ether–Et_2O for elution.

Heterocyclic Aldehydes.—Because heterocyclic aldehydes D–H were prepared as part of a larger synthetic effort, only an outline of their syntheses is given here. Preparative details and analytical data will be published later as part of the complete report.

Skraup reactions on 3-amino-1-naphthoic acid, 3-amino-2-naphthoic acid, and 4-amino-1-naphthonitrile provided benzo[*f*]quinoline-6-carboxylic acid,[17] benzo[*f*]quinoline-5-carboxylic acid,[18] and benzo[*h*]quinoline-6-carboxylic acid, respectively. Esters of these acids were reduced with $LiAlH_4$ and the resulting carbinols were oxidized to aldehydes D, E, and F, respectively. DMSO–SO_3 reagent[12] served as the oxidant that provided D and ceric ion[13] was used to provide E and F.

Aldehydes G and H were prepared from the corresponding esters by reduction to carbinols and subsequent oxidation of the alcohols with $Pb(OAc)_4$[14] and DMSO–SO_3, respectively.[12] The ester precursor to G, methyl benzo[*h*]quinoline-5-carboxylate, was obtained by photochemical ring closure of the methyl ester of β-phenyl-α-3-pyridylacrylic acid.[19] The ester precursor to H, methyl benz[*h*]isoquinoline-5-carboxylate, was obtained by a similar photoreaction employing methyl β-phenyl-α-4-pyridylacrylate.[20] The photolytic ring closures are analogous to a series reported by Loader and Timmons.[21]

(15) Melting points were obtained with a Mel-Temp appratus and are corrected. Microanalyses were performed by Miss Betty McCarthy of the Stanford Research Institute analytical laboratory. Nmr spectra were obtained on a Varian A60A instrument.

(16) This procedure is essentially that of Corey and Chaykovsky.[9]

(17) W. A. Jacobs and R. G. Gould, *J. Biol. Chem.*, **120**, 141 (1937).

(18) E. R. Barnum and C. S. Hamilton, *J. Amer. Chem. Soc.*, **64**, 540 (1942).

(19) A. R. Katritzky and A. M. Monro, *J. Chem. Soc.*, 150 (1958).

(20) D. R. Bragg and D. G. Wibberly, *ibid.*, 5074 (1961).

(21) C. E. Loader and C. J. Timmons, *ibid.*, *C*, 1078 (1964).

Antimalarials. Analogs of Phototoxic 2-Phenyl-4-quinolinemethanols[1]

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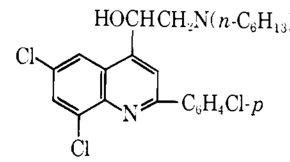
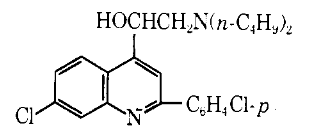
Arthur D. Little, Inc., Cambridge, Massachusetts 02140

Received June, 3, 1968

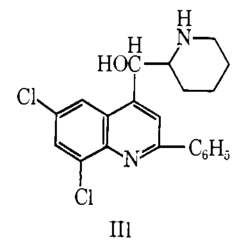
The purpose of this work was to prepare analogs of the potent antimalarials I–III,[2] two of which were observed to cause the development of sensitivity to light and other toxic symptoms that interfered seriously with their clinical use. The new compounds (Table I) include those in which chlorine was replaced by fluorine[3] and those in which the nitrogen-containing side chain



I



II



III

was derived from amines not studied previously. The pharmacology reported below indicates that, while some of these structural analogs continue to possess considerable antimalarial activity, the phototoxic side effect has not been overcome. Similar observations have been reported recently from other laboratories.[3-6]

It is now apparent that, if the phototoxic character is to be eliminated from the 2-phenyl-4-quinolinemethanol class, without at the same time decreasing the antimalarial potency, structural modifications of considerably greater sophistication must be examined; such studies are currently in progress in this and other laboratories participating in the Army Research Program on Malaria. Although some structure–activity data derived from phototoxicity studies have been reported[7] there exists a need for more fundamental data concerning the mechanism of development of phototoxic symptoms in laboratory animals and in man.

Chemistry.—The synthesis route to the compounds listed in Table I was quite similar to that described previously for the preparation of 2-phenyl-4-quinoline-

(1) This work was performed under Contract DA-49-193-MD-2901 with the U. S. Army Medical Research and Development Command, Office of the Surgeon General. Contribution No. 398 of the Army Research Program on Malaria.

(2) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. I, J. W. Edwards, Ann Arbor, Mich., 1946, pp 347, 357–358, 359.

(3) The pharmacological virtues of fluorine-containing drugs have been mentioned by A. J. Saggiomo, K. Kato, and T. Kaiya, *J. Med. Chem.*, **11**, 277 (1968).

(4) R. M. Pinder and A. Burger, *ibid.*, **11**, 267 (1968).

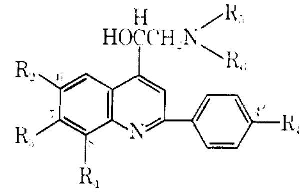
(5) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *ibid.*, **11**, 273 (1968).

(6) J. S. Gillespie, Jr., R. J. Rowlett, Jr., and R. E. Davis, *ibid.*, **11**, 425 (1968).

(7) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

TABLE I

α-(N-SUBSTITUTED AMINOMETHYL)-2-PHENYL-4-QUINOLINEMETHANOLS



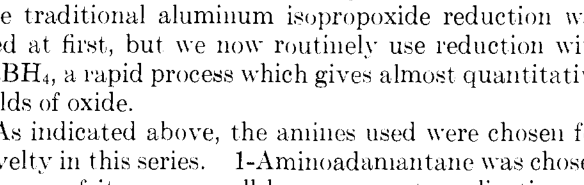
Compd	R_1	R_2	R_3	R_4	R_5	R_6	Mp, °C	Recrystn solvent	Yield,[a] %	Formula	Analyses[b]
1	Cl	H	Cl	H	H	1-Adamantyl	185–188	DMF	47	$C_{27}H_{28}Cl_2N_2O$	C, H, N
2	Cl	H	Cl	H		4-Methyl-1-piperazinyl	144–148	Hexane	34	$C_{22}H_{23}Cl_2N_3O$	H, N; C, Cl[c]
3	Cl	H	Cl	H		Morpholino	190–192	*i*-PrOH	63	$C_{21}H_{20}Cl_2N_2O_2$	C, H, Cl, N
4	Cl	H	Cl	H		4-Phenyl-1-piperazinyl	194–197	$CH_3OCH_2CH_2OH$	60	$C_{27}H_{25}Cl_2N_3O$	C, H, Cl, N
5	F	H	F	H	H	1-Adamantyl	204–207	DMF	45	$C_{27}H_{28}F_2N_2O$	C, H, F, N
6	F	H	F	H		4-Phenyl-1-piperazinyl	139–142	MeOH	29	$C_{27}H_{25}F_2N_3O$	C, H, F, N
7	F	H	F	H		Morpholino	137–140	MeOH	51	$C_{21}H_{20}F_2N_2O_2$	C, H, F, N
8	F	H	F	H		4-Methyl-1-piperazinyl	147–148	EtOH–H_2O	44	$C_{22}H_{23}F_2N_3O$	H, F; C, N[d]
9	F	H	F	H		Piperidino	163–165	EtOH	65	$C_{22}H_{22}F_2N_2O$	H, F, N; C[e]
10	F	H	F	H	*n*-C_4H_9	*n*-C_4H_9	114–119	H_2O	11	$C_{25}H_{30}F_2N_2O \cdot 2HCl$	C, H, Cl, F, N
11	F	H	F	H		See formula IV	242–245	Toluene	28	$C_{38}H_{32}F_4N_4O_2$	C, F, N
12	H	Cl	H	Cl		4-Phenyl-1-piperazinyl	212–213	DMF–H_2O	46	$C_{27}H_{25}Cl_2N_3O \cdot HCl$	C, H, Cl, N
13	H	Cl	H	Cl		Morpholino	178–181	EtOH	47	$C_{21}H_{20}Cl_2N_2O_2$	C, H, Cl, N
14	H	Cl	H	Cl	H	1-Adamantyl	183–186	DMF–H_2O	44	$C_{27}H_{28}Cl_2N_2O$	C, H, Cl, N
15	H	Cl	H	Cl		Piperidino	170–172	$CH_3OCH_2CH_2OCH_3$	52	$C_{22}H_{22}Cl_2N_2O$	C, H, Cl, N
16	H	Cl	H	Cl		4-Methyl-1-piperazinyl	166–167	*i*-PrOH	54	$C_{22}H_{23}Cl_2N_3O$	C, H, Cl, N
17	Cl	Cl	H	Cl	H	1-Adamantyl	218–221	$CH_3OCH_2CH_2OH$	32	$C_{27}H_{27}Cl_3N_2O$	C, H, Cl, N
18	Cl	Cl	H	Cl		4-Methyl-1-piperazinyl	207–210	$CH_3OCH_2CH_2OH$	33	$C_{22}H_{22}Cl_3N_3O$	C, H, Cl
19	Cl	Cl	H	Cl		4-Phenyl-1-piperazinyl	206–210 dec	$CH_3OCH_2CH_2OH$	47	$C_{27}H_{24}Cl_3N_3O$	C, H, Cl, N
20	Cl	Cl	H	Cl		Piperidino	181–184	$CH_3OCH_2CH_2OH$	51	$C_{22}H_{21}Cl_3N_2O$	C, H, Cl, N

[a] Yields reported are those of recrystallized product. No attempt was made to improve reaction or work-up conditions. [b] Values for the elements indicated were within 0.4% of theoretical. [c] C: calcd, 63.46; found, 64.16. Cl: calcd, 17.07; found, 16.21. [d] C: calcd, 68.93; found, 69.44. N: calcd, 10.97; found, 10.45. [e] C: calcd, 71.74; found, 70.76.

methanols.[8,9] We chose to prepare the quinolinemethanol drugs by the reaction of the four quinolylethylene oxide precursors with a variety of amines rather than by using the bromohydrin–amine reaction, where separation of the amine hydrobromide is necessary during isolation of the desired product.

The oxides were in turn prepared by reduction of bromomethyl ketones, followed by an alkaline work-up. The traditional aluminum isopropoxide reduction was used at first, but we now routinely use reduction with $NaBH_4$, a rapid process which gives almost quantitative yields of oxide.

As indicated above, the amines used were chosen for novelty in this series. 1-Aminoadamantane was chosen because of its many well-known recent applications in medicinal chemistry. The unconventional piperazine derivative IV was prepared by the reaction of piperazine with 2 molar equiv of oxide in a single-step reaction.



IV

We hoped to prepare compounds in the 6,8-difluoro series but we were unable to prepare 6,8-difluoro-2-phenylcinchoninic acid by the Doebner–Miller synthesis from 2,4-difluoroaniline. The only substance isolated was the typical "pyrrolidinedione anil" by-product, a class of compounds now known to possess an isomeric structure.[10] The alternative Pfitzinger synthesis failed when we were unable to convert 2,4-difluoroisonitrosoacetanilide[11] to 5,7-difluoroisatin.

Pharmacology.—Phototoxicity data previously reported[7] for **3**, **8**, **15**, **17**, and **18** in Table I show that the structural variations involved in these compounds have failed to bring about a significant reduction in phototoxicity. A more recent study of **10** by the same authors has found a minimum effective phototoxic dose of 50 mg/kg, and still other fluoro compounds in this series are known to be phototoxic.[3] It is unlikely that phototoxicity studies will be carried out with the remaining compounds in Table I.

Antimalarial activity data (Table II) for **10** supports the conclusion of others[3] that appropriate fluoro analogs are potent antimalarials; available data for **5**–**9** suggest that the nature of the amine side chain is important. The single "bis" compound studied (**11**) was inactive even at the highest doses. In the 6,8-dichloro series only **15** showed interesting activity. The expected[2] significant increase in antimalarial activity that occurred when a third chlorine atom was introduced is shown for **17**, **18**, and **20**, and a comparison of these three compounds with analogous compounds containing just two chlorine atoms shows that the type of ring substitution is a more important factor than the type of amine side chain present.

A study of our data along with those reported from other laboratories might lead to useful conclusions concerning an ideal structure for high antimalarial potency in the 2-phenyl-4-quinolinemethanol series, but all published data indicate that phototoxicity will most likely continue to be a serious undesirable side effect.

Compounds **2**, **9**, **12**, and **13** produced no significant increase in mean survival time of chicks infected with

(8) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).
(9) S. Winstein, *et al.*, *ibid.*, **68**, 1831 (1946).
(10) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 98, 1554, 1560 (1957).
(11) V. Q. Yen, N. P. Buu-Hoi, and N. D. Xuong, *ibid.*, **23**, 1858 (1958).

TABLE II

ANTIMALARIAL ACTIVITY[a]

Compd in Table I[b]	Increase in mean survival time, days, or no. of cures (C) — Dosage, mg/kg: 20	40	80	160	320	640
1	3.1	3.3	3.5	3.9	4.5	4.7
2	0.2	0.2	4.2	4.8	11.8 active	
3		0.2		0.2		1.2
6		0.2		0.4		2.0
7	0.2		0.4		0.8	2.0
8	0.2	0.4	0.4	0.8	2.4	7.4 active
9	0.4	0.8	3.0	3.6	6.0	9.6 active
10	6.2 active	7.2 active	8.5 active	1C	1C	1C
12	0.4	0.6	1.2	1.8	3.6	1C
13	0.3	0.3	0.5	0.7	3.1	6.3 active
14	2.1	2.7	3.9	4.5	6.3 active	8.5 active
15	0.1	2.9	4.7	6.7 active	8.7 active	3C
16	0.5	0.5	0.9	4.1	5.9	Toxic
17	3.9	2C	3C	4C	5C	5C
18	1.1	1C	3C	4C	5C	5C
19	0.4	0.4	0.6	1.0	2.6	
20		4.0		3C		2C, toxic

[a] Tests were carried out in five mice infected with *Plasmodium berghei* [T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)] and results were supplied by the Walter Reed Army Institute of Research, Washington, D. C. An increase in mean survival time indicates antimalarial activity. If the mean survival time is greater than twice the mean survival time (6.1 or 7.0 ± 0.5 days) of the control group, the compound is said to be "active." It is said to be "curative" (C) when an animal survives to 60 days. [b] Compounds not listed here had no significant activity.

Plasmodium gallinaceum[12] at doses up to 120 mg/kg, but **10** at 120 mg/kg produced an increase in mean survival time of 15.2 days and was rated active.

In the mosquito primary screening test[13] at concentrations of 0.1%, **5** produced at 25% sporozoite suppression and **11** a 75% sporozoite suppression; the remaining compounds were inactive (**3** and **6** were not tested).

None of the intermediates involved in our work possessed significant antimalarial activity.

Experimental Section

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., and by Dr. S. M. Nagy (M.I.T.). Satisfactory uv and ir spectra were recorded for all compounds listed in Table I.

4',7-Difluoro-2-phenylcinchoninic Acid.—*m*-Fluoroaniline, *p*-fluorobenzaldehyde, and pyruvic acid reacted under conditions similar to those used for the synthesis of the analogous dichloro compound[8] to give 40–50% yields, mp 257° (MeOH). *Anal.* ($C_{16}H_9F_2NO_2$) C, H, N, F.

4',7-Difluoro-2-phenylcinchoninoyl Chloride.—Satisfactory yields in large-scale runs were not obtained until the cinchoninic acid was first converted to its hydrochloride salt, mp 258–260°, before the reaction with $SOCl_2$. The salt was prepared by the addition of concentrated HCl to a hot solution of the cinchoninic acid in dimethoxyethane. Runs involving up to 120 g of the hydrochloride gave 60–70% yields of the acid chloride, mp 154–156° (C_6H_6), in a conventional process. *Anal.* ($C_{16}H_8F_2ClNO$) C, H, F, Cl, N.

Bromomethyl 4',7-Difluoro-2-phenyl-4-quinolyl Ketone.—The procedure described for the analogous dichloro compound[8] was used in runs involving up to 40 g of the acid chloride. The intermediate diazomethyl ketone was not characterized, and the bromomethyl ketone was isolated in 80–90% yield, either as its crude hydrobromide salt, mp 184–190°, or as the free base, mp 118–121° (HOAc–H_2O). *Anal.* ($C_{17}H_{10}BrF_2NO$) C, H, N. In some runs the diazomethyl ketone in ether suspension failed to react completely with 48% HBr, as shown by the fact that the product showed strong diazomethyl ketone absorption at 2110 and 3080 cm^{-1}. When the reaction was carried out in AcOH suspension the product was difficult to purify. Experience with another relatively stable diazomethyl ketone, to be described in a later publication, indicated that the product contained significant amounts of the debrominated substance, methyl 4',7-difluoro-2-phenyl-4-quinolyl ketone. When bromomethyl ketone containing this contaminant was subsequently reduced to the oxide (see below) the contaminant was converted to the carbinol, **4',7-difluoro-2-phenyl-4-quinolinemethanol**, mp 148–150°, isolated during the purification of the oxide. *Anal.* ($C_{17}H_{13}F_2NO$) C, H, F, N. No difficulties of this sort were encountered when the diazomethyl ketone reacted with 48% HBr in C_6H_6 suspension at room temperature; in our opinion the use of AcOH as a solvent during the reactions of diazomethyl ketones with HBr should be avoided.

Substituted 2-Phenyl-4-quinolylethylene Oxides.—The following procedure for the preparation of **4',7-dichloro-2-phenyl-4-quinolylethylene oxide** is typical of that routinely used by us in more recent work. In our early work we used Al(*i*-OPr)$_3$ reduction of the bromomethyl ketone followed by an alkaline work-up[8] of the intermediate bromohydrin, but $NaBH_4$ reduction was much more rapid and gave comparably high yields.

Bromomethyl 4',7-dichloro-2-phenyl-4-quinolyl ketone hydrobromide[8] (7.1 g, 0.015 mole) (or an equivalent quantity of free base) was suspended in 45 ml of EtOH, and 0.75 g (0.19 mole) of $NaBH_4$ was stirred in during 10 min, while maintaining the mixture at 20–25°. The suspension was stirred for 15 min longer and then a solution of 3 g of NaOH in 7.5 ml of H_2O was added. A white precipitate formed, and the suspension was stirred for 30 min. The product was washed on the filter (H_2O). The yield of dried material was usually greater than 95%. In the specific case described the product was recrystallized (Me_2CO), mp 146–147°, lit.[8] mp 143–144°. MeOH and 2-methoxyethanol were also used as solvents for the reaction; dioxane and THF were less acceptable. The reaction was carried out successfully at ten times the scale described.

4',7-Difluoro-2-phenyl-4-quinolylethylene oxide was prepared by both Al(*i*-OPr)$_3$ (91–95% yield) and $NaBH_4$ reductions, mp 124–126°. *Anal.* ($C_{17}H_{11}F_2NO$) H, F, N; C: calcd, 72.08; found, 71.56.

6,8-Dichloro-2-phenyl-4-quinolylethylene oxide was prepared only by Al(O-*i*-Pr)$_3$ reduction[8] in 97% yield, mp 184–186°. A sample for analysis had mp 190–192° (DMF). *Anal.* ($C_{17}H_{11}Cl_2NO$) H, Cl, N; C: calcd, 64.56; found, 63.67.

(12) This test was conducted by Dr. L. Rane, University of Miami. Chicks (9–12 days old) were infected with a uniform disease fatal to 100% of untreated controls within 3–4 days. Compounds under test were dissolved or suspended in peanut oil and administered subcutaneously or *per os* immediately after infection of the chicks. An increase of 100% in survival time was considered to be the minimum effective reponse to the antimalarial activity of a drug. Chicks that survived for 30 days were recorded as cured.

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

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.

Acknowledgment.—This work was suggested by Dr. R. K. Razdan of Arthur D. Little, Inc. We wish to thank Professor Robert E. Lyle and Dr. Richard E. Strube for their many helpful suggestions.

(14) K. Gerzon, V. E. Krumkalns, R. L. Brindle, F. J. Marshall, and M. A. Root, *J. Med. Chem.*, **6**, 760 (1963).

Some Characteristics of Two Bipiperidyl Mustards[1]

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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.

(1) Supported in part by U. S. Public Health Service Grant No. Ca-08485.
(2) From the Ph.D. Dissertations of Prasada Rao Koneru, 1964, and Riichiro Shibakawa, 1966.
(3) K. Gerzon, J. E. Cochran, L. A. White, R. Monahan, E. V. Krumkalns, R. E. Scroggs, and J. Mills, *J. Med. Pharm. Chem.*, **1**, 223 (1959).
(4) R. J. Rutman, F. S. Lewis, and W. D. Bloomer, *Science*, **153**, 1000 (1966).
(5) N. Yamamoto and T. Naito, *ibid.*, **150**, 1603 (1965); N. Yamamoto, T. Naito, and M. B. Shinkin, *Cancer Res.*, **26**, 2301 (1966).

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
H	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] $k_1 = \sim 3.4 \times 10^{-4}\ sec^{-1}$.

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.

(6) N. Yamamoto, private communication.
(7) Generously supplied by Eli Lilly and Co.
(8) J. C. Speakman, *J. Chem. Soc.*, 855 (1940).
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(10) A. S. Sadykov, M. Karimov, and Kh. A. Aslanov, *Zh. Obshch. Khim.*, **33**, 3414 (1963).