[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MILLIKIN UNIVERSITY, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

A New Approach to *Tertiary* β-Chloroalkylamines. Synthesis of β-Chloroalkylaminomethylhydroquinones[1]

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Several new *tertiary* β-chloroalkylamines were prepared by the action of thionyl chloride on the corresponding β-hydroxyalkylaminomethylhydroquinones obtained by the condensation of secondary β-hydroxyalkylamines with formaldehyde and hydroquinone.

Considerable interest has been shown in *tertiary* β-haloalkylamines as a result of their physiological activity. During World War II several groups of investigators[2] independently found that bis(β-haloalkyl)amines exhibited sufficient cytotoxic action to be of interest in the treatment of malignant growths. In a review of the literature on nitrogen mustards as chemical warfare agents, Sartori[3] reported that in general the toxicity decreased with an increase in the complexity of the molecule. These compounds are sometimes called radiomimetic poisons[4] since many of their physiological properties closely resemble those of ionizing radiations. More recently[5] antitumor activity was found in compounds resulting from replacement of the diethylamino substituent of chloroquine and pamaquine with a bis(β-chloroethyl)amino group.

The utility of Dibenamine, N,N-dibenzyl-β-chloroethylamine hydrochloride, as an adrenergic blocking agent earlier stimulated the study of a wide variety of related compounds. Structure activity relationships have been reviewed by Nickerson and Gump.[6] They concluded that in order to have highly specific adrenergic blocking activity, compounds related to Dibenamine must be tertiary amines having an unsaturated ring and at least one β-haloalkyl group. It has been proposed[7] that the prolonged non-competitive blockage which follows the initial effect is a result of the alkylation of some tissue in the sympathetic receptor by this intermediate.

The more general preparative methods for β-chloroalkylamines have involved either reaction of a β-hydroxyalkylamine with an alkyl halide or the reductive amination of an aryl or heterocyclic aldehyde or ketone followed by treatment with an N-alkylating or hydroxyalkylating reagent.[8] The resulting β-hydroxyalkylamines were generally converted to the corresponding β-chloro derivatives by reaction with thionyl chloride.

The reaction of phenols with formaldehyde and amines has been studied[9] extensively in our laboratories in connection with other investigations. In the present study such condensations were found to be an attractive route to 2- and 2,5-bis(β-hydroxyalkylaminomethyl)hydroquinones. Reaction of equimolar quantities of hydroquinone, formaldehyde, and bis(β-hydroxyethyl)amine at room temperature resulted in a 60% yield of 2-N,N-bis(β-hydroxyethyl)aminomethylhydroquinone. Analogous products were obtained with bis-(β-hydroxypropyl)amine, N-(β-hydroxyethyl)-methylamine and N-(β-hydroxypropyl)cyclohexylamine. The properties of these compounds are summarized in Table I.

When hydroquinone was reacted with two molar equivalents each of bis-(β-hydroxypropyl)amine and formaldehyde, two N,N-bis(β-hydroxypropyl)-aminomethyl groups were introduced into the hydroquinone nucleus. Similar results were obtained with several other representative secondary β-hydroxyalkylamines. In an amine interchange reaction, the disubstituted hydroquinone obtained with bis(β-hydroxyethyl)amine was converted in 95% yield to 2,5-bis(morpholinomethyl)hydroquinone[10] by heating with morpholine. In view of this and related work[10] the disubstituted products prepared in this study have been designated as derivatives of 2,5-bis(aminomethyl)hydroquinone. Their properties are summarized in Table I.

The β-hydroxyalkylamines were readily converted to the corresponding chloro derivatives with thionyl chloride. The properties of the β-chloroal-

(1) This paper was presented in part before the Illinois Academy of Science at Carbondale, Illinois on May 6, 1955.

(2) Gilman and Philips, *Science*, **103**, 409 (1946).

(3) Sartori, *Chem. Revs.*, **48**, 225 (1951).

(4) Philips and Thiersch, *J. Pharmacol. Exptl. Therap.*, **100**, 398 (1950).

(5) Jones, Price, and Sen, *Abstracts of Papers presented at the 129th Meeting of the American Chemical Society*, Dallas, Texas, April, 1956, page 8N.

(6) Nickerson and Gump, *J. Pharmacol. Exptl. Therap.*, **97**, 25 (1949).

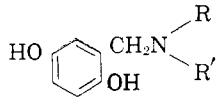
(7) Kirwin, Hall, Macko, McLean, Fellows, and Ullyot, *J. Am. Chem. Soc.*, **73**, 5681 (1951).

(8) Burger, *Medicinal Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1951, Vol. I, p. 357.

(9) Burke, *J. Am. Chem. Soc.*, **71**, 609 (1949). Burke and Weatherbee, *J. Am. Chem. Soc.*, **72**, 4691 (1950). Burke, Adams, Murdock, and Ruetman, *J. Am. Chem. Soc.*, **77**, 5637 (1955).

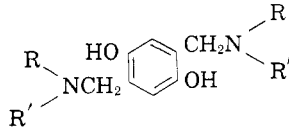
(10) Caldwell and Thompson, *J. Am. Chem. Soc.*, **61**, 2354 (1939).

TABLE I



2-(β-HYDROXYALKYLAMINOMETHYL)HYDROQUINONES

R	R′	Molecular Formula	M.p., °C.[a]	Yield, %	Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
CH_2CH_2OH	CH_2CH_2OH	$C_{11}H_{17}NO_4$	149–150[b]	60	58.13	58.22	7.54	7.42	6.17	6.15
CH_3	CH_2CH_2OH	$C_{10}H_{15}NO_3$	134–135[c]	43	60.89	60.87	7.67	7.70	7.10	7.01
$CH_2CHOHCH_3$	$CH_2CHOHCH_3$	$C_{13}H_{21}NO_4$	171–172[d]	60	61.15	61.59	8.29	8.03	5.49	5.40
C_6H_{11}	$CH_2CHOHCH_3$	$C_{16}H_{26}ClNO_3$[e]	137–139[f]	31	60.84	60.15	8.30	8.75	4.44	4.21



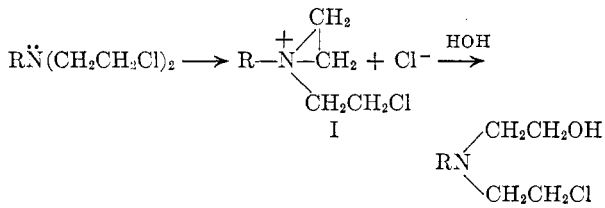
2,5-BIS(β-HYDROXYALKYLAMINOMETHYL)HYDROQUINONES

CH_2CH_2OH	CH_2CH_2OH	$C_{16}H_{28}N_2O_6$	135–136[d]	23	55.80	55.94	8.19	8.10	8.14	8.00
CH_3	CH_2CH_2OH	$C_{14}H_{24}N_2O_4$	111–112[b]	28	59.13	59.41	8.51	8.60	9.85	9.75
C_2H_5	CH_2CH_2OH	$C_{16}H_{28}N_2O_4$[h]	115–116[g]	23	61.51	61.53	9.03	9.30	8.97	8.70
$CH_2CHOHCH_3$	$CH_2CHOHCH_3$	$C_{20}H_{36}N_2O_6$[i]	188–189[b]	50	59.98	59.63	9.06	9.10	7.00	6.90
C_6H_{11}	$CH_2CHOHCH_3$	$C_{26}H_{44}N_2O_4$	197–198[b]	5	69.60	69.76	9.89	10.15	6.25	6.35

[a] Uncorrected. [b] Recrystallized from ethanol–ethyl acetate (1:1). [c] Recrystallized from ethanol–ethyl acetate (3:1). [d] Recrystallized from ethanol–ethyl acetate (3:7). [e] Isolated and characterized as the *hydrochloride*. [f] Recrystallized from acetone. [g] Recrystallized from ethanol–ethyl acetate (1:4). [h] The *picrate* of this compound melted at 213–216°; *Anal.* Calc'd for $C_{16}H_{28}N_2O_4 \cdot 2C_6H_3N_3O_7$: C, 43.65; H, 4.44; N, 14.55. Found: C, 43.83; H, 4.44; N, 14.3. [i] The *picrate* of this compound melted at 233–235°; *Anal.* Calc'd for $C_{20}H_{36}N_2O_6 \cdot 2C_6H_3N_3O_7$: C, 44.77; H, 4.92; N, 13.2. Found: C, 44.94; H, 5.05; N, 13.2.

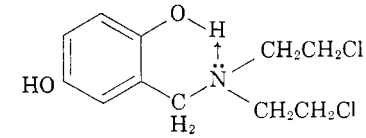
kylaminomethylhydroquinones are summarized in Table II.

Nitrogen mustards are known to be hydrolyzed readily in aqueous systems to give the corresponding dihydroxy compounds with a loss of biological activity.[11] For this reason N,N-bis(β-chloroethyl)-methylamine and related compounds are active only for a short time and within a limited site in the body. It has been proposed[2] that the pharmacological activity of these products is associated with their ability to form a highly reactive substituted ethylenimmonium ion (I), which then reacts with body tissue. If this mode of action occurs it would

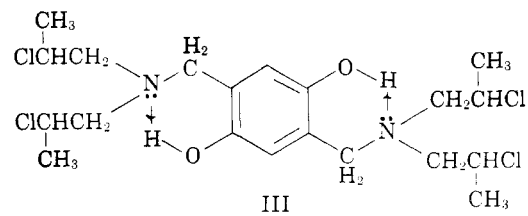


I

seem reasonable to expect that competition with the chlorine for the unshared pair of electrons of the nitrogen might produce some modification of biological action. The structures of the nitrogen mustards prepared in this work are such that the formation of a six-membered ring through hydrogen bonding is strongly favored. The proposed structures for II and III are supported by the absorption in the region of 3.2 microns shown by these compounds in infrared studies. Such hydrogen bonds might be expected to prolong physiological



II



III

activity by retarding the formation of an ethylenimmonium ion. The greater stability of these compounds as free bases as compared with other types of nitrogen mustards may be related to the hydrogen bonded structure.

Representative β-chloroalkylaminomethylhydroquinones prepared in this study are currently being tested for possible antimitotic activity.

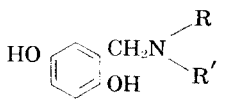
Acknowledgments. This work was supported in part by grants from the Research Corporation and from the National Science Foundation. We are also indebted to Mr. David Liu, Mr. Leo Ojakaar, and Mr. Sven Ruetman for technical assistance.

EXPERIMENTAL

2-N,N-Bis(β-hydroxyethyl)aminomethylhydroquinone. To 30 ml. of 37% aqueous formaldehyde (0.40 mole) dissolved in 50 ml. of methanol at 10° was added dropwise with agitation 42.1 g. of bis(β-hydroxyethyl)amine (0.40 mole) dissolved in 25 ml. of methanol. Hydroquinone (44 g.; 0.40

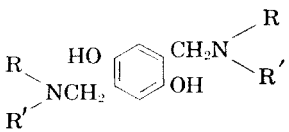
(11) Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, The Macmillan Co., New York, N. Y., 1955, p. 1415.

TABLE II



2-(β-CHLOROALKYLAMINOMETHYL)HYDROQUINONES

R	R′	Molecular Formula	M.p., °C.[a]	Yield, %	Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found	Chlorine Calc'd	Chlorine Found
CH_2CH_2Cl	CH_2CH_2Cl	$C_{11}H_{15}Cl_2NO_2$	123–125[b]	65	50.01	49.80	5.72	5.73	5.30	5.56	26.84	27.0
CH_3	CH_2CH_2Cl	$C_{10}H_{14}ClNO_2$	158 dec.[c]	45	55.68	54.81	6.54	6.67	6.50	6.79		
$CH_2CHClCH_3$	$CH_2CHClCH_3$	$C_{13}H_{19}Cl_2NO_2$	183–184 dec.[d]	43	53.43	52.91	6.55	6.71	4.79	4.80		



2,5-BIS(β-CHLOROALKYLAMINOMETHYL)HYDROQUINONES

CH_2CH_2Cl	CH_2CH_2Cl	$C_{16}H_{24}Cl_4N_2O_2$[e]	164–164.5[b]	82	45.95	45.76	5.78	5.74	6.70	6.60	33.91	33.95
CH_3	CH_2CH_2Cl	$C_{14}H_{22}Cl_2N_2O_2$	212–216 dec.[f]	65	52.34	52.05	6.90	6.94	8.72	8.65		
C_2H_5	CH_2CH_2Cl	$C_{16}H_{26}Cl_2N_2O_2$	152–153 dec.[g]	79	55.01	54.91	7.50	7.36	8.02	8.00	20.3	20.1
$CH_2CHClCH_3$	$CH_2CHClCH_3$	$C_{20}H_{32}Cl_4N_2O_2$	191–192 dec.[h]	72	50.64	50.61	6.80	6.93	5.91	5.75	29.90	29.97

[a] Uncorrected. [b] Recrystallized from petroleum ether–chloroform (2:1). [c] Recrystallized from methanol–chloroform (9:1). [d] Recrystallized from methanol–carbon tetrachloride (2:1). [e] The *hydrochloride* salt of this compound melted at 210–215° dec.; *Anal.* Calc'd for $C_{16}H_{26}Cl_6N_2O_2$: C, 39.13; H, 5.34; N, 5.70; Cl, 43.32. Found: C, 39.15; H, 5.37; N, 5.70; Cl, 42.82. [f] Recrystallized from chloroform–ethanol (1:5). [g] Recrystallized from ethanol. [h] Recrystallized from ethanol–ethyl acetate (1:1).

mole) was added and the resulting solution was kept at 25–28° in the dark for 18 hours. The solvents were removed under reduced pressure on a water-bath at 40–50°. The residue crystallized when kept at 10–15°. Upon recrystallization from ethyl acetate-ethanol (1:1) solution 25 g. (60% yield) of nearly white product was obtained, m.p. 149–150°.

Anal. Calc'd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.17. Found: C, 58.22; H, 7.42; N, 6.15.

The same compound was obtained when the above reaction mixture was refluxed gently for two hours instead of allowing it to stand for 18 hours at 25–28°. Similar results were obtained when the aqueous formaldehyde was replaced by 12 g. of paraformaldehyde (0.4 mole) dissolved in 50 ml. of methanol containing approximately 0.05 g. of potassium hydroxide.

The *picrate* melted at 202–203° after recrystallization from 95% ethanol.

Anal. Calc'd for $C_{11}H_{17}NO_4 \cdot C_6H_3N_3O_7$: N, 12.28. Found: N, 12.20.

2,5-Bis[N,N-(bis-β-hydroxypropyl)aminomethyl]hydroquinone. To 30 ml. of 37% aqueous formaldehyde (0.4 mole) dissolved in 50 ml. of methanol at 10° was added 53.2 g. of bis(β-hydroxypropyl)amine (0.4 mole) dissolved in 50 ml. of methanol, with stirring over a period of five minutes. Hydroquinone (22 g.; 0.2 mole) was added with shaking and after 17 hours at 25–28° the solvents were removed under reduced pressure at 50°. The resulting thick sirup was dissolved in 10 ml. of hot ethyl acetate. A white solid (26 g.) separated upon cooling; m.p. 181–185°. An additional 14.7 g. of product (m.p. 178–181°) was obtained from the filtrate; yield 50%. The compound was recrystallized from a mixture of equal volumes of ethyl acetate and ethanol; m.p. 188–189°.

Anal. Calc'd for $C_{20}H_{36}N_2O_6$: C, 59.98; H, 9.06; N, 7.0. Found: C, 59.63; H, 9.10; N, 6.9.

2,5-Bis(morpholinomethyl)hydroquinone by amine interchange. A solution of 2.0 g. of 2,5-bis[N,N-(bis-β-hydroxyethyl)aminomethyl]hydroquinone in 10 ml. of morpholine was heated under gentle reflux for 24 hours. Morpholine was removed under reduced pressure from the reaction mixture at 40–60° until solid began to precipitate. After addition of 15 ml. of ethanol and cooling, the resulting crystalline product (1.6 g.) was removed by filtration and washed with ethanol; m.p. 203.5–205.5°. An additional 0.15 g. was obtained from the filtrate; yield 95%. The product melted at 205–206° after recrystallization from methanol and did not depress the m.p. of 2,5-bis(morpholinomethyl)-hydroquinone (lit.[12] m.p. 205°) prepared directly from hydroquinone, formaldehyde, and morpholine.

2-N,N-Bis(β-chloroethyl)aminomethylhydroquinone. To 9.08 g. of 2-N,N-bis(β-hydroxyethyl)aminomethylhydroquinone (0.04 mole) in a 300-ml. round-bottom flask in an ice-bath was added through a reflux condenser 10 ml. of thionyl chloride. The temperature was gradually raised to 35° and an additional five ml. of thionyl chloride was added. After 30 minutes the excess thionyl chloride was removed under reduced pressure and the resulting fluffy solid was dissolved in 100 ml. of water. After filtration the salt was converted to the free base by addition of 2-aminoethanol dropwise to the filtrate until no further product separated. The sticky mass hardened upon standing and was removed by filtration; yield 6.81 g. (64.5%), m.p. 123–125° after recrystallization from chloroform–petroleum ether (2:1 by volume).

Anal. Calc'd for $C_{11}H_{15}Cl_2NO_2$: C, 50.01; H, 5.72; N, 5.30; Cl, 26.84. Found: C, 49.80; H, 5.73; N, 5.56; Cl, 27.0.

2,5-Bis[N,N-bis(β-chloropropyl)aminomethyl]hydroquinone. To 3.1 g. of 2,5-bis[N,N-bis(β-hydroxypropyl)aminomethyl]-hydroquinone was added 16.5 g. of thionyl chloride dropwise with shaking. The reaction mixture was gently refluxed for 15 minutes. The resulting solid product was stirred with 200 ml. of water and the insoluble material was removed by filtration. 2-Aminoethanol was added to the filtrate until a cloudiness just began to appear and then an additional ml. of reagent was added. The white precipitate was removed by filtration. The total yield was 2.63 g. (71.6%), m.p. 191–196° (dec.). The product melted at 191–192° (dec.) after recrystallization from a mixture of equal volumes of ethanol and ethyl acetate.

Anal. Calc'd for $C_{20}H_{32}Cl_4N_2O_2$: C, 50.64; H, 6.80; N, 5.91; Cl, 29.90. Found: C, 50.61; H, 6.93; N, 5.75; Cl, 29.97.

Infrared absorption spectra. A Perkin-Elmer Model 21 spectrophotometer equipped with a sodium chloride prism was used. The samples were observed as mulls in Nujol.

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(12) Bruson, U. S. Patent 2,040,040 (1936).