PHENOLIC MANNICH BASES

CARL WEATHERBEE, RICHARD P. RYAN, JR., JAN F. BRANTHAVER,
and GAROLD E. GOKEN
Millikin University, Decatur, Illinois

ABSTRACT.—The synthesis of several 2-bis (beta-hydroxyethyl) aminomethyl-p-substituted phenols, 2-bis(beta-hydroxypropyl)aminomethyl-p-substituted phenols, and their conversion to the corresponding nitrogen mustards, is reported.

DISCUSSION

In previous work (Weatherbee, 1956, p. 1138) condensation of equimole quantities of hydroquinone, formaldehyde, and N,N-iminodiethanol in methanol solution resulted in the isolation of a 60% yield of 2-N,N-Bis (beta-hydroxyethyl) aminomethylhydroquinone, but only a 23% yield of 2,5-Bis [N,N-bis (beta-hydroxyethyl) aminomethyl] hydroquinone was secured upon the interaction of hydroquinone, formaldehyde, and N,N-iminodiethanol in a 1:2:2 mole ratio, respectively.

In continuation of this work the condensations of *p*-substituted phenols, formaldehyde, and bis (beta-hydroxyalkyl) amines were investigated. Details of the experimental work are given at the end of this paper.

Reaction of *p-tert*-butylphenol, formaldehyde, and N,N-iminodiethanol in a mole ratio of 1:1:1 gave a salt of the expected Mannich base, 2-bis (beta-hydroxyethyl) aminomethyl-p-*tert*-butylphenol-hydro-*p-tert*-butylphenolate. The expected Mannich base apparently reacted stoichiometrically with the *p-tert*-butylphenol. Similarly when bis (beta-hydroxypropyl) amine was used in lieu of the N,N-iminodiethanol, the stoichiometric addition compound of 2-bis (beta-hydroxypropyl) aminomethyl-4-*tert*-butylphenol with *p-tert*-butylphenol was the only crystalline product isolated.

In view of the salt formation, condensations were carried out in alcoholic hydrochloric acid solutions; low yields of the Mannich base hydrochlorides or starting materials were obtained. Addition of dry hydrogen chloride to reaction mixtures of equimole quantities of amine, formaldehyde, and phenol after the usual reaction time without the removal of the solvents resulted in the isolation of tars and viscous materials. However, removal of the solvent from the condensation of *p*-substituted phenols, formaldehyde, and bis (beta-hydroxylalkyl) amines in methanol at 25° for 20 hours or at gentle refluxing for 2 hours gave oils. When the oils were dissolved in methanol followed by the addition of dry hydrogen chloride, the Mannich base hydrochlorides were secured. By use of this procedure the average yields of 2,5-Bis [N,N-bis (beta-hydroxyethyl) aminomethyl] hydroquinone were increased from 23% to over 60%, and the yields of other previously reported derivatives of hydroquinone (Weatherbee, 1956, p. 1138) were increased.

The hydroquinone derivative, 2,5-Bis [N,N-bis (beta-hydroxyethyl) aminomethyl] hydroquinone, was used as an intermediate in the preparation of 2,5-Bis [N,N-bis (beta-chloroethyl) aminomethyl] hydroquinone hydrochloride, which is effective against Ca 755, L1210, Dunning Leukemia, Lymphoma 8, Ehrlich EF, Yoshida Hepatoma; and Walker 256 ascites, pulmonary and solid substaneous (Wilson, 1961, p. 199). Mannich bases prepared in this work have been submitted to the National Institutes of Health for evaluation against Walker 256 rat tumors, KB cell culture, and their routine three tumor-bearing animal screens (lymphoid Leukemia 1210, Adenocarcinoma 755, and Sarcoma 180).

The usual procedure (Raiziss, 1941, p. 3124) (Speziale, 1956, p. 2556) for converting beta-hydroxyalkyl amines to their corresponding beta-chloro derivatives with thionyl chloride involves the addition of the latter to a solution of the hydroxy alkylamines in chloroform, methylene chloride, benzene, or other inert solvent, followed by refluxing. The use of diethylene glycol dimethyl ether as a solvent has also been reported (Lyttle, 1958, p. 80). Only small yields of phenolic nitrogen mustards from the 2-bis (beta-hydroxyalkyl) amines were secured by this procedure. It was found convenient to add the thionyl chloride dropwise to the solid beta-hydroxyalkyl amine hydrochloride on an ice bath and permitting the reaction mixture to slowly warm to room temperature. In certain instances the reaction mixture was warmed to 35-40° after the addition of the thionyl chloride, but temperatures in excess of 40° resulted in the formation of tars and noncrystalline materials. Addition of thionyl chloride to the free bases (beta-hydroxyalkyl amines) gave somewhat lower yields than when the amine hydrochlorides were employed.

Reaction of 2-bis (beta-hydroxyethyl) aminomethyl-4-benzyloxyphenol with thionyl chloride at 30-35° resulted in the isolation of 2-bis (beta-chloroethyl) aminomethylhydroquinone hydrochloride rather than the desired 2-bis (beta-chloroethyl) aminomethyl-4-benzyloxyphenol-hydrochloride, the thionyl chloride or hydrogen chloride formed during the reaction readily cleaved the benzyloxy group.

PROCEDURES

The C, H microanalyses were performed by Weiler and Strauss, Microanalytical Laboratory, Oxford, England. The N analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium im Max-Planck-Institut fur Kohlenforschung, Ruhr, Germany. The temperatures are reported in degrees centigrade.

2,5-Bis [bis (beta-hydroxyethyl) aminomethyl] hydroquinone dihydrochloride.—To 420.6 g (4 mole) of N,N-iminodiethanol in 100 ml of methanol at 14-17° was added dropwise with stirring 216.2 g of 55% formaldehyde (4 mole) in methanol. After adding 220 g (2 mole) of hydroquinone, the mixture was stirred well for 5 minutes. The resulting solution was warmed at 30-40° for 2 hours and then at 45-50° for 2 hours. The solvents were removed by vacuum and the resulting oil was dissolved in 150 ml of methanol. Dry hydrogen chloride was bubbled through the solution until no further precipitate appeared to form. Upon filtration 470 g of white solid was secured. An additional 38 g was obtained by concentrating the filtrate at room temperature. Total crude yield was 508 g (60%), m.p. 198-200° (dec). After 4 recrystallizations from 90% methanol-water solution, the product melted at 208-209° (dec). (Analysis: Calculated for $C_{16}H_{30}Cl_2N_2O_6$: C, 46.05; H, 7.24. Found: C, 46.35; H, 7.36).

2-Bis (beta-hydroxyethyl) aminomethyl-4-tert-butylphenol hydro-p-tert-butylphenolate.—To 7.5 ml of 37% formaldehyde (0.1 mole) was added with stirring over a period of 3 minutes 9.6 ml of N,N-iminodiethanol (0.1 mole) dissolved in 10 ml methanol at 15-16°. After adding 15 g of *p-tert*-butylphenol (0.1 mole) in 25 ml of methanol, the mixture was stirred for 5 minutes at 15-18° and then set aside in a stoppered flask for 22 hours at 25-28°. The solvents were removed by evaporation under a hood leaving a reddish-brown solid. Upon recrystallization from cyclohexane, the product weighed 15 g (72%), m.p. 97-99°. Two additional recrystallizations gave m.p. 100-101°. (Analysis: Calculated for $C_{15}H_{25}NO_3 \cdot HOC_6H_4C(CH_3)_3$: C, 71.90; H, 9.41; N, 3.36. Found: C, 71.73; H, 9.46; N, 3.20, 3.34).

2-bis(beta-hydroxypropyl)aminomethyl-4-tert-butylphenol-hydro-p-tert-butylphenolate. — Repetition of the above experiment using bis(beta-hydroxypropyl)amine in lieu of the iminodiethanol gave a 68% yield of 2-bis(beta-hydroxypropyl)aminomethyl-4-tert-butylphenol-hydro-p-tert-butylphenolate, m.p. 111-112°. (Analysis: Calculated for $C_{17}H_{29}NO_3$ $HOC_6H_4C(CH_3)_3$: C, 72.77; H, 9.73; N, 3.14. Found: C, 72.34, 73.19; H, 9.52, 9.66; N, 3.01, 3.17).

2-bis(beta-chloroethyl)aminomethyl-4-tert-butylphenol hydrochloride.—To 10 g (0.035 mole) of 2-bis (beta-hydroxyethyl)aminomethyl-4-*tert*-butylphenol hydrochloride cooled on an ice bath was added dropwise 15 ml of thionyl chloride. The mixture was allowed to slowly warm to room temperature and stand for 14 hours. The excess thionyl chloride was removed by vacuum leaving a viscous material which was dissolved in 20 ml of ethyl acetate containing a trace of ethyl alcohol. Upon cooling 9.2 g (75%) solid, m.p. 120-123° was removed by filtration. Three recrystallizations from ethyl acetate containing a trace of ethyl alcohol gave m.p. 140-142°. (Analysis: Calculated for $C_{15}H_{23}Cl_2NO \cdot HCl$: C, 52.87; H, 7.10; Ionic Cl, 10.40; N, 4.11. Found: C, 53.03; H, 7.36; Ionic Cl, 10.70; N, 4.04).

The following compounds were prepared under conditions similar to the formation of 2,5-bis(beta-hydroxyethyl)aminomethyl hydroquinone dihydrochloride:

2-bis(beta-hydroxyethyl)aminomethyl-4-
bromophenol hydrochloride, m.p. 158°,
yield 70%. Analysis: Calculated for
$C_{11}H_{16}BrNO_3 \cdot HCl$: C, 40.45; H, 5.24;
ionic Cl, 10.85. Found: C, 40.72; H, 5.33;
ionic Cl, 11.04.

2-bis(beta-hydroxyethyl)aminomethyl-4
tertiarybutylphenol hydrochloride, m.p
162-164°, yield 58%. Analysis: Calcu
lated for $C_{15}H_{25}NO_3 \cdot HCl$: C, 59.30; H
8.63; ionic Cl, 11.67; N, 4.61. Found
C, 59.64; H, 8.66; ionic Cl, 11.82; N, 4.41

2-bis(beta-hydroxyethyl)aminomethyl-
tertiaryamylphenol hydrochloride, m.
145°, yield 61%. Analysis: Calculate
for $C_{16}H_{27}NO_3 \cdot HCl$: C, 60.46; H, 8.8
ionic Cl, 11.16; N, 4.40. Found: C, 60.5
H, 8.63; ionic Cl, 11.35; 11.17; N, 4.43.

2-bis(beta-hydroxyethyl)aminomethyl-4-benzyloxyphenol hydrochloride, m.p. 168°, yield 51%. Analysis: Calculated for $C_{18}H_{23}NO_4 \cdot HCl$: C, 61.10; H, 6.84; ionic Cl, 10.02. Found: C, 60.84; H, 7.13; ionic Cl, 10.27.

2-bis(beta-hydroxypropyl)aminomethyl-4-tertiarybutylphenol hydrochloride, m.p. 208-210°, yield 41%. Analysis: Calculated for $C_{17}H_{29}NO_3 \cdot HCl$: C, 61.52; H, 9.11; ionic Cl, 10.68. Found: C, 61.75; H, 9.00; ionic Cl, 10.91.

2-bis(beta-hydroxypropyl)aminomethyl-4-tertiaryamylphenol hydrochloride, m.p. 191-193°, yield 49%. Analysis: Calculated for $C_{18}H_{31}NO_3 \cdot HCl$: C, 62.50; H, 9.33; ionic Cl, 10.25; N, 4.05. Found: C, 62.44; H, 9.45; ionic Cl, 10.05; N, 4.00.

2-bis(beta-hydroxypropyl)aminomethyl-4-benzyloxyphenol hydrochloride, m.p. 171-173°, yield 37%. Analysis: Calculated for $C_{20}H_{27}NO_4 \cdot HCl$: C, 62.90; H, 7.39; ionic Cl, 9.29. Found: C, 62.71; H, 7.45; ionic Cl, 9.40.

The following compounds were prepared under conditions similar to the formation of 2-bis(beta-chloroethyl)aminomethyl-4-tertiarybutylphenol hydrochloride:

2-bis(beta-chloroethyl)aminomethyl-4-bromophenol hydrochloride, m.p. 175-176°, yield 78%. Analysis: Calculated for $C_{11}H_{14}BrCl_2NO \cdot HCl$: C, 36.34; H, 4.16; ionic Cl, 9.75; N, 3.85. Found: C, 36.11; 36.29; H, 4.23, 4.08; ionic Cl, 9.61; N, 4.14.

2-bis(beta-chloroethyl)aminomethyl-4-tertiaryamylphenol hydrochloride, m.p. 116-117°, yield 82%. Analysis: Calculated for $C_{16}H_{25}Cl_2NO \cdot HCl$: C, 54.32; H, 7.13; ionic Cl, 10.02; total Cl, 30.07. Found: C, 53.78, 54.65; H, 7.61, 7.79; ionic Cl, 10.32; total Cl, 29.35.

2-bis(beta-chloroethyl)aminomethyl-4-hydroxyphenol hydrochloride, m.p. 215-216°, yield 70%. Analysis: Calculated for $C_{11}H_{15}Cl_2NO_2 \cdot HCl$; C, 43.95, H, 5.37. Found: C, 44.41, H, 5.44.

2-bis(beta-chloropropyl)aminomethyl-4-tertiarybutylphenol hydrochloride, m.p. 162-163°, yield 59%. Analysis: Calculated for $C_{17}H_{27}Cl_2NO \cdot HCl$: C, 55.37; H, 7.65; ionic Cl, 9.62; N, 3.78. Found: C, 55.14; H, 7.84; ionic Cl, 9.70; N, 3.64.

2-bis(beta-chloropropyl)aminomethyl-4-tertiaryamylphenol hydrochloride, m.p. 150-152°, yield 73%. Analysis: Calculated for $C_{18}H_{29}Cl_2NO \cdot HCl$: C, 56.47; H, 7.90; ionic Cl, 9.26; total Cl, 27.79. Found: C, 56.10, 56.70; H, 7.62, 8.09; ionic Cl, 9.43; total Cl, 27.7.

ACKNOWLEDGMENTS

The authors wish to thank the National Science Foundation Undergraduate Science Education Program and the National Institutes of Health (Grant Number CA-07115-01) for assistance in this work. We also acknowledge the technical assistance of Ulrich Klabunde, Janet Walmsley (Hamilton), and Peter Zung-Jih Han.

LITERATURE CITED

LYTTLE, D. A., and H. G. PETERING. 1958. 5-bis-(alpha-chloroethyl) aminouracil. A New Antitumor Agent. J. Am. Chem. Soc. 80: 6459.

RAIZISS, G. W., and L. W. CLEMENCE. 1941. 2-Sulfanilyl-aminothiazoline. J. Am. Chem. Soc. 63: 3124.

SPEZIALE, A. J., and P. C. HAMM. 1956. Preparation of Some New 2-Chloroacetamides. J. Am. Chem. Soc. 78: 2556.

WEATHERBEE, C., R. TEMPLE, and W. J. BURKE. 1956. A New Approach to Tertiary beta-Chloroalkylamines. Synthesis of beta-Chloroalkylaminomethylhydroquinones. J. Org. Chem. 21: 1138.

WILSON, W. L., and ROBERT B. GREEN. 1961. Weatherbee Mustard. Cancer Chemotherapy Reports 12: 199.

Manuscript received February 10, 1964