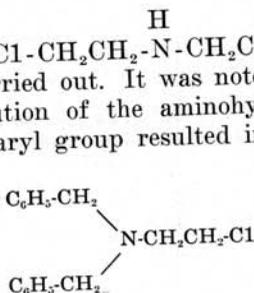


SOME MANNICH REACTIONS

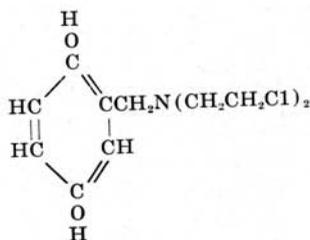
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INTRODUCTION

During World War II considerable investigation of the nitrogen mustards, Cl-CH₂CH₂-N-CH₂CH₂-Cl, was carried out. It was noted that substitution of the aminohydrogen by an aryl group resulted in a decrease of toxic properties, as did the substitution of one of the beta-



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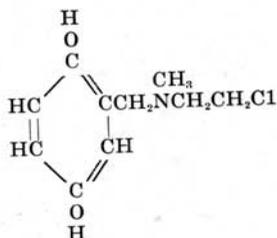
chloroethyl groups with either an aryl or an alkyl group. Dibenamine, for example, has been found to have

considerable applications of therapeutic interest.

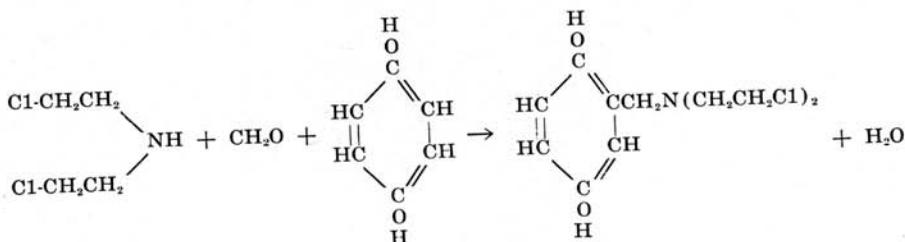
DISCUSSION

In this investigation some new compounds related to dibenamine or to the nitrogen mustards have been prepared by Mannich-type reactions. Examples of these compounds are bis(chloroethyl) aminomethylhydroquinone, bis(2 chloropropyl)-aminomethylthydroquinone, and methyl-beta-chloroethylamino-methylhydroquinone.

It is believed that these compounds could be obtained by condensation of such compounds as

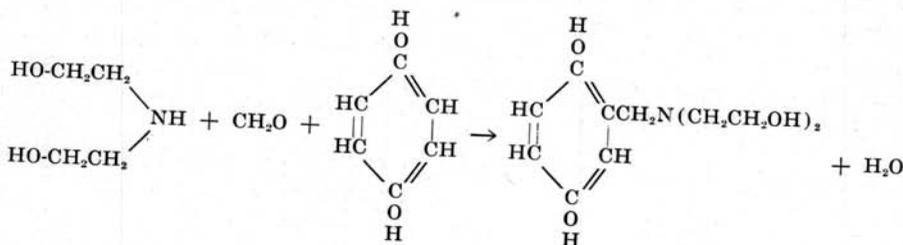


“nitrogen mustard” (beta, beta-dichloroethylamine), formaldehyde, and hydroquinone.



In order to avoid use of the toxic beta, beta-dichloroethylamines, beta-hydroxyethylamines, formaldehyde, and hydroquinone were condensed

37% aqueous formaldehyde (0.4 mole) dissolved in 50 ml. of methanol at 10° was added 53.2 gms. (0.4 mole) diisopropanolamine dis-

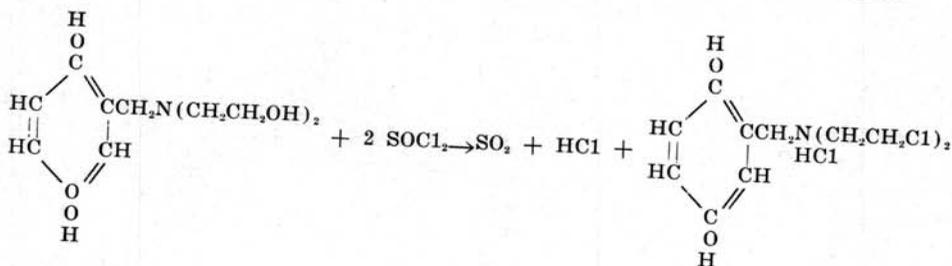


to give the corresponding beta-hydroxyethylaminomethylhydroquinones.

The latter compounds were readily converted to the desired betachloroethylaminomethylhydroquinones with thionyl chloride.

When a molar ratio of 2:2:1 for the amines, formaldehyde, and

solved in 50 ml. methanol, slowly, with stirring over a period of 5 minutes. The resulting solution was shaken for several seconds and 22 gms. hydroquinone (0.2 mole) was added batchwise. The flask was shaken until each addition of hydroquinone dissolved. The stoppered flask was placed in a dark drawer



hydroquinone was employed, 2,5-bis-(beta-hydroxyethylaminomethyl)-hydroquinones were isolated.

These compounds are now being investigated for toxic and physiological properties.

EXPERIMENTAL

The experimental procedure followed in this investigation is illustrated by the following examples: 2,5-bis(*N,N*-diisopropanolaminomethyl)hydroquinone. — To 30 ml.

at 25 to 28° for 17 hours. The resulting liquid was concentrated at 50° at 30 mm./Hg until white crystals began to appear. The syrupy mass was washed into an Erlenmeyer flask with 10 ml. ethyl acetate. After warming the mixture at the boiling point for several minutes, the flask was stoppered and placed in the refrigerator at 10° for 24 hours. A white solid separated and was removed by filtration; after

drying in a desiccator it weighed 26 gms., m.p. 181-185°. The filtrate was concentrated, yielding an additional 14.7 gms. of white solid, m.p. 178-181°. Total crude yield was 40.7 gms. or 50%. A sample was recrystallized 5 times for analysis from a 50-50 mixture of ethyl acetate-ethanol, m.p. 188-189°.

Analysis: Calculated for $C_{20}H_{36}N_2O_6$: C, 59.97; H, 9.05; N, 7.00
: C, 60.29; H, 9.24; N, 6.8

Found

2,5-bis (N,N-betachloropropyl) aminomethyl hydroquinone.—To 3.1 gms. (0.0077 mole) 2,5-bis (beta-hydroxypropyl) aminomethyl hydroquinone in a flask attached to a reflux condenser was added 16.5 gms. (0.139 moles) thionyl chloride, dropwise with shaking. The resulting mixture was gently refluxed for 15 minutes, until the mixture turned solid. The contents of the flask were washed into a beaker with 200 ml. water; after stirring, a curdy precipitate was removed by filtration and discarded. To the clear yellowish filtrate was added monoethanolamine until a cloudiness just began to appear and then 1 ml. additional monoethanolamine was added. The flask was shaken and allowed to stand for 10 minutes while a curdy, white precipitate formed. The precipitate was removed by filtration and the filtrate treated with additional monoethanolamine without effect. The dried solid weighed 2.63 gms., m.p. 191-196°(dec); yield 71.6%. A sample was recrystallized three times for analysis, m.p. 191-192°(dec).

Analysis: Calculated for $C_{20}H_{32}Cl_4N_2O_2$: C, 50.64; H, 6.80; N, 5.91; Cl, 29.90
: C, 50.61; H, 6.93; N, 5.75; Cl, 29.97

Found

SUMMARY

A new series of beta-hydroxyethyl-amonomethylhydroquinones and beta-chloroethylaminomethylhydroquinones have been synthesized. The latter compounds are similar to compounds known to have desirable physiological properties and are cur-

rently being investigated for toxicity as well as physiological activity.

ACKNOWLEDGMENTS

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