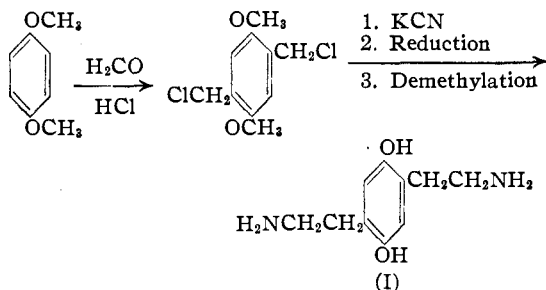


[CONTRIBUTION NO. 55 FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF TENNESSEE]

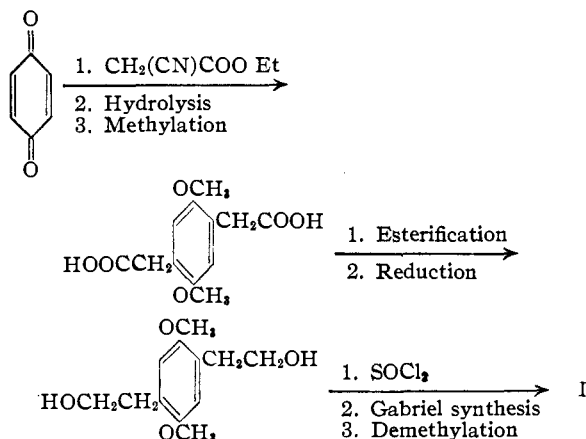
Di-( $\alpha$ - and  $\beta$ -Substituted Aminoethyl)-benzenes. I. 2,5-bis-(2-Aminoethyl)-hydroquinones<sup>1</sup>By J. H. WOOD AND ROGER E. GIBSON<sup>1a</sup>

The aminoethyl function is a component common to a large number of physiologically active compounds. In the benzene nucleus, it gives rise to a series of compounds noted for their sympathomimetic activity, benzedrine and ephedrine being familiar examples. Studies so far made among these compounds relating structure with activity have been concerned with introducing substituents on the  $\alpha$ - and  $\beta$ -carbons, on the nitrogen and in the ring of the parent  $\beta$ -phenylethylamine. We have prepared for pharmacologic activity study a series of new compounds in which the  $\beta$ -aminoethyl function is repeated in a para relationship. Additional interest on our part in these compounds is occasioned by our need for them as intermediates in the preparation of certain heterocyclic types.

The parent of the series reported in this paper, 2,5-bis-(2-aminoethyl)-hydroquinone, I, was synthesized by two independent paths, as follows



The second method, important in the proof of structure, gave poor yields



The methods of preparation, analyses, and conversion into known compounds serve to characterize the new amines and their intermediates.

(1) Presented at the 114th meeting of the American Chemical Society, St. Louis, Missouri, September, 1948.

(1a) University of Tennessee Fellow, 1947-48.

Pressor, bronchodilator and antihistamine activity tests, made by The Lilly Research Laboratories of Eli Lilly and Company on the hydrochloride salts of I and its O-methyl, N-dimethyl and O-methyl-N-dimethyl derivatives, revealed that these amines are inactive in these respects. They showed less than 10% "Egotrate" activity. Since the introduction of a second  $\beta$ -aminoethyl function does not significantly alter the chemical properties of the molecule the loss of activity must be ascribed to other effects. It is planned to continue this study by preparing and testing the activity of derivatives in which the positions of the aminoethyl functions are varied as well as the substituents on their  $\alpha$ - and  $\beta$ -carbon atoms.

Experimental<sup>2</sup>

**2,5-bis-(Chloromethyl)-hydroquinone Dimethyl Ether.**—The following is an adaptation of Brunner's<sup>3</sup> general method for the chloromethylation of aromatic compounds. To a stirred solution of 103 g. (0.75 mole) of the dimethyl ether of hydroquinone, 600 ml. of dioxane and 100 ml. of concentrated hydrochloric acid was added three 50 ml. portions of 40% formalin (2 moles) at thirty-minute intervals. During the period of addition, hydrogen chloride gas was passed through. Stirring and the introduction of hydrogen chloride gas were continued for three hours longer and then 450 ml. of concentrated hydrochloric acid was added. After cooling, the solid material which had formed was removed by filtration and allowed to dry. One recrystallization from acetone gave 135 g. (77%) of white, crystalline material that melted at 163-164°. Further purification, which was unnecessary for most purposes, gave a product which melted at 167.5°. Brunner reported the melting point as about 165°.

*Anal.* Calculated for  $\text{C}_{10}\text{H}_{12}\text{O}_2\text{Cl}_2$ : Cl, 30.16. Found: Cl, 30.14.

**2,5-bis-(Cyanomethyl)-hydroquinone Dimethyl Ether.**—To a hot, stirred solution of 300 ml. of ethylene glycol monoethyl ether, 500 ml. of acetone and 117.5 g. (0.5 mole) of 2,5-bis-(chloromethyl)-hydroquinone dimethyl ether, in a reflux apparatus, was added slowly an aqueous solution containing 97.5 g. (1.5 moles) of potassium cyanide in 125 ml. of warm water. After refluxing four hours, the hot mixture was filtered. The residue consisted of a mixture of potassium chloride and the cyanomethyl compound. The filtrate, upon cooling in an ice-bath, deposited additional cyanomethyl compound in the form of grayish crystals. After filtering, the mother liquor was used to extract the cyanomethyl compound from potassium chloride in the residue obtained from the first filtration. This extraction was repeated (usually three times) until no solid was obtained upon cooling the filtered, hot extracting solution. The combined residues of the cyanomethyl compound, after washing with methanol, weighed 68 g., m. p. 193-195°. Recrystallization from dioxane gave 59 g. (54.5%) of white, crystalline material, m. p. 195-196.5°, which was pure enough for our work. A small portion was further purified for analysis and melted at 198°.

*Anal.* Calculated for  $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2$ : N, 12.96. Found: N, 12.99.

(2) All melting points are corrected.

(3) Brunner, U. S. Patent 1,887,396 (1933).

**2,5-Dimethoxy-*p*-benzenediacetic Acid Diethyl Ester.**—A solution of 225 g. (0.88 mole) of 2,5-dimethoxy-*p*-benzenediacetic acid<sup>4</sup> (prepared from the hydroquinone<sup>5</sup>), 2 l. of absolute ethanol, and 750 ml. of benzene was placed in a 3-l. flask fitted with stirrer and a 75-cm. Vigreux column equipped with a variable take-off. Esterification was accomplished by keeping the solution saturated with hydrogen chloride gas over a four-hour reflux period during which time the low-boiling fraction was continuously removed. The volume of the reaction mixture was then increased to about 4 l. by the addition of 95% ethanol, heated to boiling and filtered. Upon cooling, the ester separated as grayish crystals which were removed by filtration. Evaporation of the filtrate to about one-third of its volume and cooling yielded an additional amount. Total yield of crude ester was 210 g. (76.5%). Further purification was achieved by recrystallization from alcohol and gave a colorless, crystalline material, m. p. 115.5°.

*Anal.* Calculated for C<sub>18</sub>H<sub>22</sub>O<sub>6</sub>: C, 61.92; H, 7.15. Found: C, 61.78; H, 7.11.

**2,5-bis-(2-Hydroxyethyl)-hydroquinone Dimethyl Ether.**—To 150 g. (6.5 g. atoms) of melted sodium dispersed in hot xylene contained in a 3-liter flask fitted with stirrer and condenser was slowly added a warm solution of 250 ml. of xylene and 500 ml. of absolute butanol containing 140 g. (0.45 mole) of 2,5-dimethoxy-*p*-benzenediacetic acid diethyl ester. Xylene was added at intervals in sufficient quantities to prevent the reaction mixture from setting to a gel. The mixture was then heated with stirring until all sodium had dissolved. Water was added and the mixture was steam distilled until the xylene and butanol had been removed. Upon cooling to 0°, 40 g. (39%) of the slightly impure alcohol separated. Recrystallization from water with decolorization gave white crystals, m. p., 133.5–134°.

*Anal.* Calculated for C<sub>12</sub>H<sub>18</sub>O<sub>4</sub>: C, 63.69; H, 8.02. Found: C, 63.39; H, 8.12.

Acidification of the mother liquor from the above reaction yielded 54 g. of the acid formed by the hydrolysis of the unreduced ester.

**2,5-bis-(2-Aminoethyl)-hydroquinone Dimethyl Ether.**—Method No. 1: Into a steel bomb of 600-ml. capacity were placed 25 g. (0.12 mole) of 2,5-bis-(cyanomethyl)-hydroquinone dimethyl ether, 250 ml. of absolute ethanol saturated with ammonia, and about 10 g. of Raney nickel catalyst. After introducing hydrogen to a pressure of 1,900 lb./sq. in., the bomb was placed in the heating jacket of a hydrogenation apparatus and shaken at 120° for forty-five minutes. The pressure fall was very rapid the first fifteen minutes. After cooling, the contents were removed, filtered, and the filtrate evaporated under reduced pressure on the steam-bath, leaving a red oil. This oil was distilled at 150–155° at a pressure of less than 1 mm., using a very short path still with a large side arm. About 20 g. (77%) of the pure amine was thus obtained as a white, crystalline solid. The amine proved to be very basic, removing carbon dioxide from air. Freshly prepared, it melted at about 90°. Upon standing in air, its melting point changed very rapidly. It, as well as its sulfonamide and hydrochloride, proved to be identical with the amine obtained by method 2.

Method No. 2: A small excess of thionyl chloride was added to a mixture of 10 g. (0.044 mole) of 2,5-bis-(2-hydroxyethyl)-hydroquinone dimethyl ether and 100 ml. of dry ethyl ether. After carefully warming for a few minutes, the mixture was slowly evaporated to dryness on the steam-bath. The chloride thus presumably formed was not purified. Potassium phthalimide, 20 g. (0.11 mole), was added, a small air condenser attached, and the mixture heated for eight hours at 160–170° with occasional stirring. After cooling, the solid product was broken up and about 175 ml. of alcohol and 15 ml. of 40% hydrazine hydrate were added. After heating one hour

on the steam-bath, excess hydrochloric acid was added and the mixture filtered. The filtrate was evaporated to about 100 ml. and then refiltered. The filtrate was made alkaline with excess sodium hydroxide and then boiled a few minutes to expel any hydrazine present. After extracting with ether, the amine was precipitated as the salt by passing hydrogen chloride into the ether solution. The yield was about 10%. The amine thus obtained was identical with the one obtained in method 1.

The dihydrochloride salt, a white, hygroscopic solid, melted at 335° dec.

*Anal.* Calculated for C<sub>12</sub>H<sub>22</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>2</sub>: Cl, 23.86. Found: Cl, 23.91.

The benzenesulfonamide derivative was a white, crystalline solid after recrystallization from alcohol, m. p., 195.5°.

*Anal.* Calculated for C<sub>24</sub>H<sub>28</sub>O<sub>6</sub>N<sub>2</sub>S<sub>2</sub>: N, 5.55. Found: N, 5.60.

**2,5-bis-(2-Aminoethyl)-hydroquinone.**—A solution of 15 g. (0.067 mole) of 2,5-bis-(2-aminoethyl)-hydroquinone dimethyl ether in 100 ml. of 48% hydrogen bromide was refluxed eight hours. Upon cooling, the amine hydrobromide precipitated as a tan material. Evaporation of the mother liquor to about one-third of its former volume gave a small additional amount. After drying to remove excess hydrogen bromide, the salt was dissolved in 80 ml. of water. The free amine was then obtained as a gray solid upon adding excess sodium bicarbonate. This phenolic amine, while stable in acidic solutions, was unstable in alkali solutions, its solution in sodium hydroxide rapidly forming a black precipitate. The amine freshly precipitated with sodium bicarbonate from an aqueous solution of the recrystallized hydrochloride salt was a slightly colored solid, m. p. 234° dec., soluble in alcohol, ether, acids and bases.

The dihydrochloride was prepared by adding a small amount of water to the gray solid obtained above and then adding an excess of concentrated hydrochloric acid. Upon evaporating to 75 ml. and cooling, the salt precipitated. After washing with absolute alcohol and then ether, the salt was twice recrystallized from an alcohol-water mixture to give 7 g. (39%) of a white, crystalline solid, m. p. 313° dec.

*Anal.* Calculated for C<sub>10</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>2</sub>: Cl, 26.35. Found: Cl, 26.25.

**N,N'-Tetramethyl-2,5-bis-(2-aminoethyl)-hydroquinone Dimethyl Ether.**—This compound was prepared by the method of Icke, Wisegarver and Alles<sup>5</sup>: 22.4 g. (0.1 mole) of 2,5-bis-(2-aminoethyl)-hydroquinone dimethyl ether yielded the crude tertiary amine in the form of a red oil. This was distilled at 133–135° at less than 1 mm. to give 17.5 g. (62.5%) of a white, crystalline solid, m. p. 51–52°, soluble in alcohol and ether. A Hinsberg test indicated a tertiary amine.

The dihydrochloride melted at 275° dec.

*Anal.* Calculated for C<sub>18</sub>H<sub>30</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>2</sub>: Cl, 20.07. Found: Cl, 19.97.

**N,N'-Tetramethyl-2,5-bis-(2-aminoethyl)-hydroquinone.**—This compound was prepared in a manner analogous to that described above for 2,5-bis-(2-aminoethyl)-hydroquinone. The free amine obtained from the hydrochloride salt was a light brown solid, m. p. 178, which darkened upon standing in air, and was soluble in ether, alcohol, acids and bases. The yield of pure hydrochloride was about 38%.

The dihydrochloride salt, m. p. 278° dec., was a white, crystalline solid.

*Anal.* Calculated for C<sub>14</sub>H<sub>26</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>2</sub>: Cl, 21.80. Found: Cl, 21.92.

## Summary

1. Procedures have been developed for synthesizing phenolic derivatives containing two

(4) Icke, Wisegarver and Alles, "Organic Syntheses," **25**, 89 (1945).

(4) Wood, Colburn, Cox and Garland, *THIS JOURNAL*, **66**, 1541 (1944).

(5) Wood and Cox, "Organic Syntheses," **26**, 24 (1946).

$\beta$ -aminoethyl functions in a para relationship.

2. Pressor, bronchodilator and antihistamine activity tests have been made on the amines.

3. Several new compounds intermediate in the formation of the amines are reported.

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[CONTRIBUTION FROM WESTERN REGIONAL RESEARCH LABORATORY<sup>1</sup>]

## Ethers of *p*-Hydroxydiphenylamine as Alkyl Halide Identification Derivatives

BY DAVID F. HOUSTON

The preparation of several ethers of *p*-hydroxydiphenylamine as intermediates for other syntheses drew attention to their value as derivatives for the identification of alkyl halides. These ethers offer an alternative choice to previously reported<sup>2,3,4,5</sup> derivatives.

The hydroxydiphenylamine is commercially available and can be readily purified. The synthesis of the ethers was convenient, and the products were easily crystallized. Ether formation from primary halides was general. *s*-Butyl chloride gave unreacted amine together with oil and tarry matter. Tertiary halides were not investigated. Mixtures of two ethers with closely similar melting points showed melting-point depressions of several degrees.

Data on the ethers are collected in the accompanying table. The melting points follow the usual trend for a homologous series, and those for the even-carbon alkyl ethers above the hexyl compound follow a smooth curve.

collecting the product distilling at 170–180°. The dark still residue contained some diphenyl-*p*-phenylenediamine. Final recrystallizations from benzene-hexane gave material melting at 69–70° in agreement with the reported<sup>7</sup> value of 70°. Less rigorous purification may be satisfactory, as indicated by the fact that the octyl ether prepared directly from the commercial *p*-hydroxydiphenylamine, though remaining somewhat dark colored, melted at 45.5–46.2° in complete agreement with the analytical sample from the purified amine.

*n*-Propyl and *n*-amyl iodides, heptyl bromide, and *s*-butyl and benzyl chlorides were obtained from Eastman Kodak Company. The hexyl, octyl, dodecyl and hexadecyl bromides were research-grade chemicals (boiling within a two degree range) obtained from a commercial supplier of halogen chemicals. *n*-Butyl bromide had been prepared and fractionally distilled in this Laboratory.

The isopropoxydiphenylamine was a commercial product. It was distilled at reduced pressure, and the portion distilling at 140–145° at 1.5 mm. was purified by decolorizing a methanol solution with charcoal and crystallizing the product from aqueous methanol (1:3).

**Procedure.**—Preparation of the ethers, essentially the same in all cases, is illustrated by synthesis of the *n*-propyl compound. Equivalent amounts (0.02 mole) of *p*-hydroxydiphenylamine (3.70 g.) and *n*-propyl iodide (2.46

TABLE I

*p*-HYDROXYDIPHENYLAMINE ETHERS,  $\text{ROC}_n\text{H}_4\text{NHC}_6\text{H}_5$

Halide used	M. p., °C.	Empirical formula	Analytical data, %					
			Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
<i>n</i> -Propyl iodide	62.2–62.9	C <sub>15</sub> H <sub>17</sub> NO	79.26	79.4	7.54	7.55	6.16	6.06
Isopropyl <sup>a</sup>	86.3–87.1	C <sub>15</sub> H <sub>17</sub> NO	79.26	79.3	7.54	7.56	6.16	6.12
<i>n</i> -Butyl bromide	46.9–47.3	C <sub>16</sub> H <sub>19</sub> NO	79.63	79.6	7.94	7.90	5.80	5.80
<i>n</i> -Amyl iodide	40.9–41.3	C <sub>17</sub> H <sub>21</sub> NO	79.96	80.2	8.29	8.31	5.49	5.46
<i>n</i> -Hexyl bromide	41.0–41.5	C <sub>18</sub> H <sub>23</sub> NO	80.25	80.4	8.60	8.59	5.20	5.18
<i>n</i> -Heptyl bromide	44.9–45.3	C <sub>19</sub> H <sub>25</sub> NO	80.52	80.5	8.89	8.92	4.94	4.89
<i>n</i> -Octyl bromide	45.5–46.3	C <sub>20</sub> H <sub>27</sub> NO	80.76	80.9	9.15	9.03	4.71	4.69
<i>n</i> -Dodecyl bromide	61.3–61.9	C <sub>24</sub> H <sub>35</sub> NO	81.53	81.6	9.98	9.88	3.96	3.94
<i>n</i> -Hexadecyl bromide	74.5–75.3	C <sub>28</sub> H <sub>49</sub> NO	82.10	82.2	10.57	10.44	3.42	3.39
Benzyl chloride	95.2–95.8	C <sub>19</sub> H <sub>17</sub> NO	82.88	82.9	6.22	6.17	5.09	5.08

<sup>a</sup> Purified from commercial product; see text.

### Experimental

**Materials.**—The *p*-hydroxydiphenylamine was a sample of commercial product with a stated 92% purity. It was further purified by distillation with superheated steam,<sup>6</sup>

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) L. L. Merritt, Jr., S. Levey and H. B. Cutter, *THIS JOURNAL*, **61**, 15 (1939).

(3) R. D. Drew and J. M. Sturtevant, *ibid.*, **61**, 2666 (1939).

(4) W. M. Lauer, P. A. Sanders, R. M. Leekley and H. E. Ungnade, *ibid.*, **61**, 3050 (1939).

(5) H. B. Cutter and H. R. Golden, *ibid.*, **69**, 831 (1947).

(6) A. A. Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, pp. 144–145.

g.) were added to 18 cc. of 10% alcoholic potassium hydroxide (0.03 equivalent). The solution was refluxed three hours with stirring by magnetic stirrer, cooled, diluted to 200 cc. with water, acidified slightly with hydrochloric acid, and chilled to 0°. The dark solids were filtered off, and decolorized with charcoal in 85 cc. of alcohol. The filtrate was diluted with water to clouding, cooled to 0°, and again filtered. The yield at this point was 2.78 g. (61%). Two recrystallizations from aqueous alcohol gave pearly flakes melting at 40.9–41.3° (cor.).

The halides used, and the melting points and analytical data for the ethers formed, are presented in the table.

**Acknowledgment.**—I wish to express my appreciation to E. B. Kester for his interest in this

(7) A. Calm, *Ber.*, **16**, 2799 (1883).