[CONTRIBUTION NO. 91 FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF TENNESSEE]

Bis-(2-aminoethyl)-benzenes. II. 1,2- and 1,3-Bis-(2-aminoethyl)-benzenes[1]

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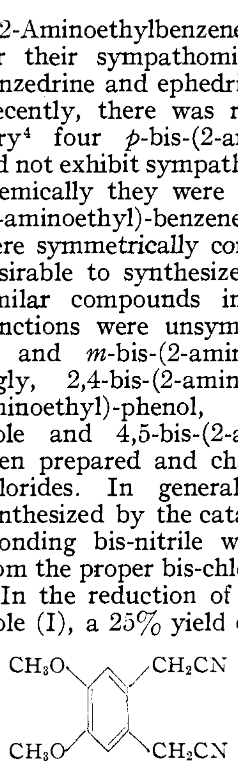
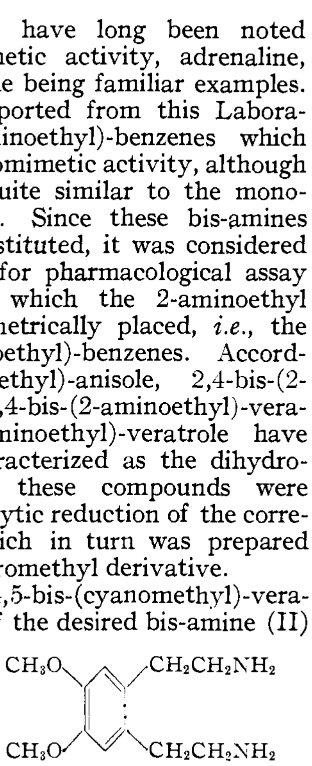
Some unsymmetrical bis-(2-aminoethyl)-benzenes and a benzazepine have been prepared and characterized. These amines have been pharmacologically assayed by the Eli Lilly and Company.

2-Aminoethylbenzenes have long been noted for their sympathomimetic activity, adrenaline, benzedrine and ephedrine being familiar examples. Recently, there was reported from this Laboratory[4] four *p*-bis-(2-aminoethyl)-benzenes which did not exhibit sympathomimetic activity, although chemically they were quite similar to the mono-(2-aminoethyl)-benzenes. Since these bis-amines were symmetrically constituted, it was considered desirable to synthesize for pharmacological assay similar compounds in which the 2-aminoethyl functions were unsymmetrically placed, *i.e.*, the *o*- and *m*-bis-(2-aminoethyl)-benzenes. Accordingly, 2,4-bis-(2-aminoethyl)-anisole, 2,4-bis-(2-aminoethyl)-phenol, 3,4-bis-(2-aminoethyl)-veratrole and 4,5-bis-(2-aminoethyl)-veratrole have been prepared and characterized as the dihydrochlorides. In general, these compounds were synthesized by the catalytic reduction of the corresponding bis-nitrile which in turn was prepared from the proper bis-chloromethyl derivative.

In the reduction of 4,5-bis-(cyanomethyl)-veratrole (I), a 25% yield of the desired bis-amine (II) was obtained along with a 38% yield of a lower boiling amine whose analysis corresponded to that of two isomeric substances, a benzazepine (III) and an aminohydrindene (IV). A compound analogous to the latter was obtained by von Braun, Kruber and Danziger[5] by the chemical reduction of 1,2-bis-(cyanomethyl)-benzene. However, the Hinsberg and nitrous acid tests indicated that the amine in question was a secondary one and consequently supported the structure of the azepine. Further, total methylation gave a mono-methyl derivative rather than a dimethyl one. The amine, therefore, has been assigned the structure of 7,8-dimethoxy-1,2,4,5-tetrahydrobenz[d]azepine.


I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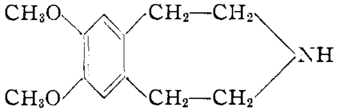
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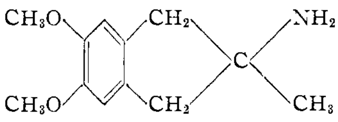
IV

Pharmacological testing of the amine hydrochlorides was done by the Lilly Research Laboratories of Eli Lilly and Company. While all of these bis-amines, in contrast to the similar *p*-bis-(2-aminoethyl)-benzenes which were inactive, did exhibit some sympathomimetic acitivity, as well as other types of activity, the activity was considerably less than that generally exhibited by mono-(2-aminoethyl)-amines. It would appear, therefore, that a second 2-aminoethyl group causes a loss of activity, the loss being greatest when the two groups are para to each other.

Experimental

2,4-Bis-(cyanomethyl)-anisole.—To a hot, stirred solution of 61.5 g. (0.30 mole) of 2,4-bis-(chloromethyl)-anisole[6] in 200 ml. of acetone and 100 ml. of ethylene glycol monoethyl ether was added a solution of 58.5 g. (0.90 mole) of potassium cyanide in 85 ml. of warm water at such a rate as to maintain gentle refluxing. Refluxing and stirring were continued for four hours. After distilling off 160 ml. of acetone, the hot solution was transferred to a 1-l. separatory funnel, and the solid precipitate was dissolved in a small quantity of cold water and added to the separatory funnel. To this mixture was added an additional 500 ml. of water. The mixture was extracted with three 250-ml. portions of ether, and the ether extract was washed four times with 100-ml. portions of water to remove ethylene glycol monoethyl ether. The ether extract was dried over magnesium sulfate and then allowed to evaporate. Needles and an oil resulted. After filtering and washing with cold methanol, the crystalline product was recrystallized twice from methanol. There resulted 28.5 g. (51%) of slightly yellow product melting at 72.0–72.5°. Repeated attempts to decolorize with charcoal failed to remove the slight yellow color or to change the melting point.

Anal. Calcd. for $C_{11}H_{10}ON_2$: N, 15.05. Found: N, 14.95.

4,5-Bis-(cyanomethyl)-veratrole.—To a hot solution of 60 g. (0.255 mole) of 4,5-bis-(chloromethyl)-veratrole[6] in 335 ml. of acetone and 140 ml. of ethylene glycol monoethyl ether was added slowly a solution of 50 g. (0.77 mole) of potassium cyanide in 80 ml. of warm water. Then refluxing and stirring were continued for four hours. The solution was filtered while hot, and the residue was washed with acetone until devoid of color. These washings were added to the filtrate, and this mixture was boiled in the hood to remove acetone and hydrogen cyanide. The nitrile was then obtained in a dry ether extract as previously described. After removal of the ether by spontaneous evaporation, the residual oil was submitted to distillation under reduced pressure. After an initial forerun amounting to about 3 g. and consisting mainly of ethylene glycol monoethyl ether, a white oil with a faint green fluorescence distilled at 205–212° (6 mm.). This oil solidified to a white solid on standing. Recrystallization from absolute ethanol gave 11 g. (20%) of a white crystalline product which melted at 120–121°. A second recrystallization from methanol resulted in no change in melting point.

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: N, 12.96. Found: N, 13.20.

3,4-Bis-(cyanomethyl)-veratrole.—To a refluxing solution of 200 ml. of acetone, 120 ml. of ethylene glycol mono-

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[1] Presented at the 118th Meeting of the American Chemical Society, Chicago, Illinois, September, 1950.

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[4] J. H. Wood and R. E. Gibson, THIS JOURNAL, **71**, 393 (1949).

[5] J. von Braun, O. Kruber and E. Danziger, *Ber.*, **49**, 2642 (1916).

[6] J. H. Wood, M. A. Perry and C. C. Tung, THIS JOURNAL, **72**, 2989 (1950).

ethyl ether and 50 g. (0.212 mole) of 3,4-bis-(chloromethyl)-veratrole[6] was added slowly a solution of 41 g. (0.63 mole) of potassium cyanide in 100 ml. of water at 75°. Refluxing and stirring were continued for three hours. The mixture was filtered, and the precipitate was washed with ether. The ether washings were added to the filtrate, along with 500 ml. of water. The crude nitrile was then obtained by extracting with ether in the manner previously described. The resulting solid material was recrystallized from ethanol after decolorizing with charcoal to give 33 g. of semi-white needles, m.p. 87–88.5°. One more recrystallization from methanol gave 29.8 g. (65%) of white needles, m.p. 88.5–89.0°.

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: N, 12.96. Found: N, 12.86.

2,4-Bis-(2-aminoethyl)-anisole.—Twenty-five grams (0.135 mole) of 2,4-bis-(cyanomethyl)-anisole, with 100 ml. of ethanol, saturated with ammonia, and about 10 g. of freshly prepared Raney nickel catalyst, was hydrogenated in a stainless steel bomb with shaking at 120° and an initial hydrogen pressure of 1800 p.s.i. at 20° until the pressure drops indicated that the theoretical amount of hydrogen had been taken up (about 90 minutes). After removing catalyst and solvent, the remaining green oil was distilled at reduced pressure from a short path still to give 14 g. (54%) of a clear, colorless oil, b.p. 160–161° (1 mm.). This amine had a fishy odor and was quite basic.

Dihydrochloride.—The amine was dissolved in anhydrous ether, and hydrogen chloride was introduced into the solution with vigorous shaking. The white solid which precipitated was removed, washed on the filter with ether and acetone, and dried. Recrystallization from absolute alcohol gave a product which melted with decomposition at 195–196°.

Anal. Calcd. for $C_{11}H_{20}ON_2Cl_2$: Cl, 26.54. Found: Cl, 26.43.

2,4-Bis-(2-aminoethyl)-phenol Dihydrobromide.—To 100 ml. of 48% hydrobromic acid at 0°, 12 g. (0.062 mole) of 2,4-bis-(2-aminoethyl)-anisole was added slowly. The resulting solution was refluxed for eight hours. On cooling, a brown solid separated and was collected. After concentrating the filtrate, a small additional quantity was obtained. This material was washed twice with ether and dried by suction, giving 14 g. (66%) of the crude dihydrobromide. One gram of the crude hydrobromide was recrystallized twice from absolute ethanol giving 250 mg. of a semi-white crystalline solid, m.p. 265–268° dec.

Anal. Calcd. for $C_{10}H_{18}ON_2Br_2$: Br, 46.72. Found: Br, 46.02.

Dihydrochloride.—Twelve grams of 2,4-bis-(2-aminoethyl)-phenol dihydrobromide was dissolved in 75 ml. of concd. hydrochloric acid. After evaporating to 50 ml., the solution was allowed to cool in the ice-chest. The dihydrochloride precipitated out as a brown salt which was then redissolved in 50 ml. of concd. hydrochloric acid and the process repeated in order to remove traces of the hydrobromide not converted by the first treatment. The precipitated hydrochloride was recrystallized with difficulty from ethanol to give 8.9 g. (21.3%) of white crystalline salt, m.p. 248–249° dec.

Anal. Calcd. for $C_{10}H_{18}ON_2Cl_2$: Cl, 28.01. Found: Cl, 28.35.

3,4-Bis-(2-aminoethyl)-veratrole.—A mixture of 6.0 g. (0.028 mole) of 3,4-bis-(cyanomethyl)-veratrole, about 5 g. of Raney nickel, and 100 ml. of absolute ethanol saturated with ammonia was hydrogenated as previously described. After removing catalyst and solvent, the resulting oil was submitted to distillation under reduced pressure, yielding 5 g. (81%) of a clear, colorless oil, b.p. 139–141° (1 mm.). This oil failed to solidify on cooling to 0°. It was found to be soluble in water and in acids but insoluble in basic solutions. A Hinsberg test on the amine indicated a primary amine, the resulting sulfonamide being an oil which was soluble in sodium hydroxide.

Dihydrochloride.—Five grams (0.022 mole) of 3,4-bis-(2-amino-ethyl)-veratrole was dissolved in 200 ml. of absolute ether, and hydrogen chloride was introduced into the solution until precipitation of the amine salt was complete. The precipitate was removed by filtration and then washed repeatedly with absolute ether and finally with cold absolute ethanol. The material was dried at 80° under 20 mm. pressure. From this procedure was obtained 6.25 g. (95%) of a white solid that decomposed at 228–232°.

Anal. Calcd. for $C_{12}H_{22}O_2N_2Cl_2$: Cl, 23.86. Found: Cl, 23.71.

4,5-Bis-(2-aminoethyl)-veratrole.—Nineteen grams of 4,5-bis-(cyanomethyl)-veratrole was hydrogenated at 120° in the manner previously described. The contents of the bomb were removed and filtered to remove the spent catalyst. The catalyst was washed with three portions of absolute ethanol, the washings being added to the filtrate. Condensation of the volume of the resulting liquid to about 40 ml. resulted in a dark, oily liquid which was distilled *in vacuo*. From this distillation there was obtained, two fractions. One fraction, amounting to 7 g. (38%), was obtained in the form of a colorless oil, b.p. 153–155° (1 mm.), which solidified on standing, m.p. 87–88°. The higher boiling fraction, b.p. 175–176° (1 mm.), amounted to 5 g. (25.4%) and proved to be the desired amine. It failed to solidify on cooling in the ice-chest but gave a positive test for a primary amine by the Hinsberg procedure.

Dihydrochloride.—The hydrochloride formed by passing hydrogen chloride into an ether solution of the amine was washed several times with absolute ether and then dried at 75° under a pressure of 15 mm. One recrystallization from ethanol gave a white solid (91%), m.p. 257–262° dec.

Anal. Calcd. for $C_{12}H_{12}O_2N_2Cl_2$: Cl, 23.86. Found: Cl, 23.20.

7,8-Dimethoxy-1,2,4,5-tetrahydrobenz[d]azepine.—The lower boiling fraction obtained by the distillation of the reduction products of the 4,5-bis-(cyanomethyl)-veratrole was further purified by recrystallization from absolute ethanol to yield a white, crystalline, secondary amine (38%), m.p. 94–95°. The hydrochloride, formed by passing hydrogen chloride into an ether solution of the amine, was recrystallized from absolute ethanol; yield 95%, m.p. 243–245° dec.

Anal. Calcd. for $C_{12}H_{18}O_2NCl$: Cl, 14.55; N, 5.76. Found: Cl, 14.65; N, 5.75.

Acetyl Derivative.—Two grams (0.01 mole) of the free amine was dissolved in 20 ml. of 20% sodium hydroxide by heating. After cooling the mixture, 5 ml. of acetic anhydride was added in 0.5-ml. portions with vigorous shaking and cooling under the water tap. The gray solid material that formed during this operation was collected on filter paper and then recrystallized twice from water to give 1.3 g. (52%) of the acetyl derivative as white crystals, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{14}H_{19}O_3N$: N, 5.62. Found: N, 5.71.

Methyl Derivative.—Total methylation was achieved by the method of Icke, *et al.*[7] Upon acidification of the reaction mixture and then evaporating to dryness at reduced pressure, the crude salt was obtained as a yellow solid. After three recrystallizations from alcohol, a white, crystalline solid was obtained, m.p. 359–361° dec. The free amine was obtained by dissolving the hydrochloride in a small amount of water, adding a small excess of sodium hydroxide, and then extracting the mixture with ether. Upon evaporating to dryness, a white crystalline solid, m.p. 40–41.5°, was obtained (over-all yield, 60%).

Acknowledgment.—The authors are indebted to Eli Lilly and Company for the pharmacological assays and for financial aid to one of us. We are also indebted to the Tennessee Eastman Corporation for financial aid to one of us.

KNOXVILLE, TENNESSEE RECEIVED APRIL 23, 1951

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[7] R. N. Icke, B. B. Wisegarver and G. A. Alles, *Org. Syntheses*, **25**, 89 (1945).