

UNITED STATES PATENT OFFICE

2,653,977

BIS-(SUBSTITUTED-PHENYLALKYL-AMINO)-COMPOUNDS

Paul N. Craig, Elkins Park, and Fred P. Nabenhauer, Philadelphia, Pa., assignors to Smith, Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

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6 Claims. (Cl. 260—570.5)

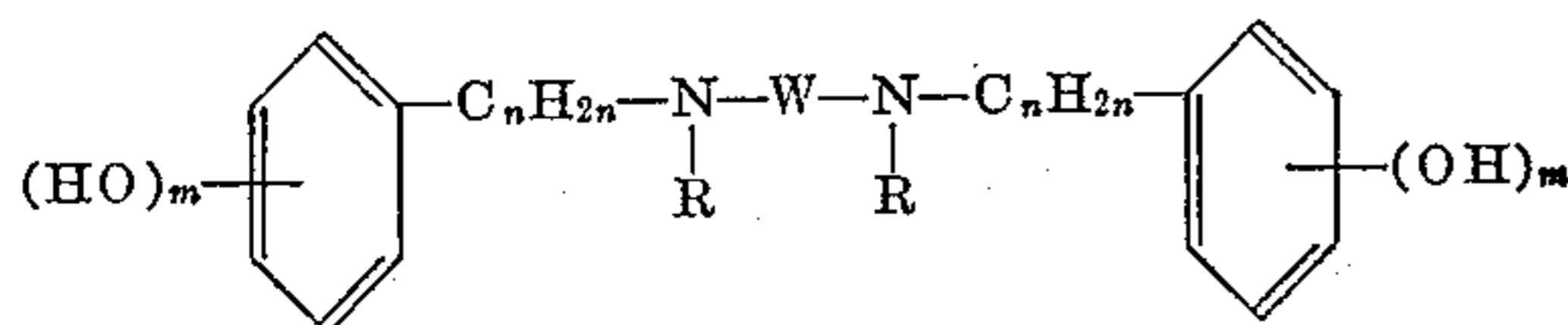
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This invention relates to certain new chemical compounds, a new class of bis-(substituted-phenylalkylamino) compounds, possessing physiological activity; and more particularly, relates to a series of bis-(hydroxyphenylalkylamino)-bridge compounds and their acid addition salts, which have utility as blood pressure agents possessing long duration of action, and are variously hyper- and hypotensive.

It is an object of this invention to provide a series of orally active agents for treatment of abnormal blood pressure conditions.

It is a further object of this invention to provide a series of orally active agents having a prolonged duration of action for treatment of abnormal blood pressure conditions.

The free bases of the compounds according to this invention are represented by the following general formula:



in which:

m is either 2 or 3; n is an integer from 1-6 inclusive; R is selected from the group consisting of hydrogen and lower alkyl; W is a bridging member selected from the group consisting of alkylene of not more than 14 carbon atoms, alkylene-phenylene-alkylene of from 8-16 carbon atoms, alkylene-oxy-alkylene of from 4-14 carbon atoms, alkylene-thio-alkylene of from 4-14 carbon atoms, alkylene-amino-alkylene of from 4-14 carbon atoms, alkylene-alkylamino-alkylene of from 5-21 carbon atoms, and alkylene-aralkyl-amino-alkylene of from 11-23 carbon atoms.

In a publication by Goodson et al. in the Brit. J. Pharm. 3, 49 (1948), there are disclosed certain compounds similar to those of the instant application. The disclosed compounds were tested for toxicity and in vivo and in vitro amoebicidal activity. Most of the compounds are irritants and all are very toxic. Some of the compounds exhibited greater toxicity when administered orally than when administered subcutaneously. Subcutaneous administration produces local necrosis and after oral administration irreparable damage to intestinal walls was observed.

The organic and inorganic salts contemplated by this invention include, by way of example, salts of the bases formed with organic acids such as for example, glycolic, oxalic, maleic, camphorsulfonic, acetic, tartaric, etc., and inorganic acids

2

such as, for example, sulfamic, hydrochloric, hydrobromic, sulfuric, phosphoric and the like.

Generally speaking, to prepare the hydroxy-substituted compounds of this invention, the correspondingly substituted methoxy- or benzyloxy-substituted phenylalkylamine is utilized as a starting material. This is done in order to protect the existence of the ultimate hydroxy groups, against destruction or removal during succeeding reactions. As a final step in preparing these compounds then, the protective groups such as methyl or benzyl are removed by procedures well-known in the art, producing the hydroxy substituted compounds desired. The appropriate methoxy- or benzyloxy-substituted phenylalkylamine is reacted with the desired dihalide in the presence or absence of a solvent. The ratio of the phenylalkylamine to the dihalide may be varied from 2:1 to 10:1 or more, as desired. Solvents which may be used are alcohols such as, for example, methanol, ethanol, isopropanol, and the like and hydrocarbons such as, for example, benzene, toluene or xylene, or any inert solvent which will not react with the reagents. The reaction may be carried out at varied temperatures from 20° C. to 150° C., as desired.

As an alternate method of preparation the desired dibasic acid and an excess of the appropriate methoxy- or benzyloxy-substituted phenylalkylamines are reacted according to the method of Hahn and Gudjons, Ber. 71, 2186 (1938). The N,N-bis-(substituted phenylalkyl)-amide formed is reduced by means of lithium aluminum hydride to the corresponding secondary amine.

The methoxy- or benzyloxy-substituted phenylalkylamines, dihalides, and dibasic acids used in the preparation of the key intermediates are either well known to the art or are prepared by methods analogous to those reported in the literature.

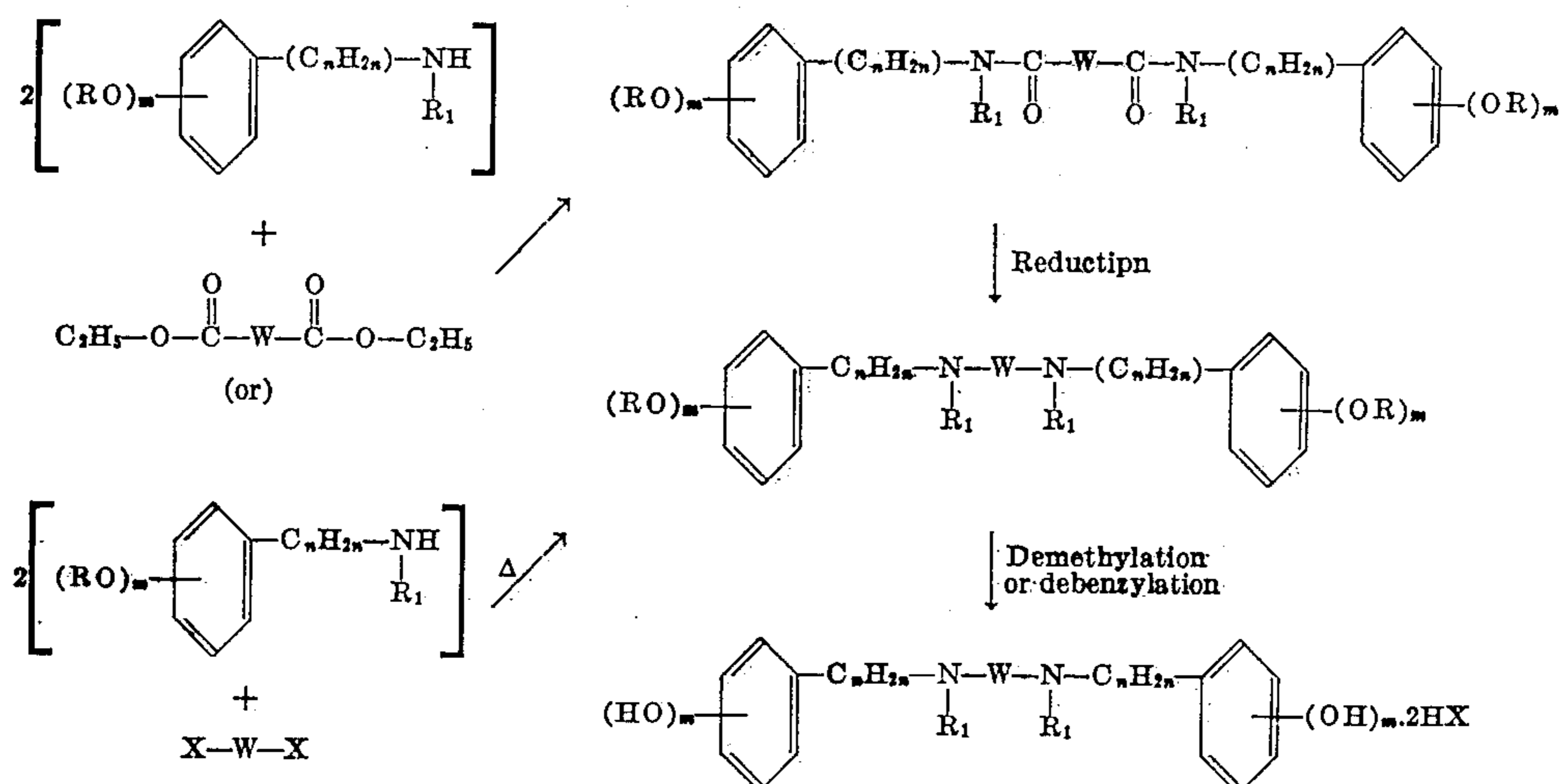
For those cases in which the final product is a tertiary amine, a secondary phenylalkylamine may be used in the condensation reaction with the dihalide. Or alternately, the tertiary amino group may be introduced by alkylation of the bis-secondary amino intermediates before demethylation or debenzylation. This alkylation is carried out by procedures well known to those skilled in the art using standard alkylating reagents, such as, for example, alkyl halides, aralkyl halides, alkyl benzene sulfonates and the like.

The removal of the oxygen-protecting group by demethylation or debenzylation, as may be the case, to provide the corresponding OH-substituted product is effected by standard techniques such as, heating with constant boiling

3

hydrobromic acid in the presence of a trace of hypophosphorous acid or using hydrogen and a palladium-charcoal catalyst, respectively. In debenzylating, the acid addition salts are usually used.

The method of preparation of these compounds will be made apparent by the following reaction:



in which:

m is either 2 or 3; n is an integer from 1-16 inclusive; R is selected from the group consisting of methyl and benzyl; R_1 is selected from the group consisting of hydrogen and lower alkyl; W is a bridging member selected from the group consisting of alkylene of not more than 14 carbon atoms, alkylene-phenylene-alkylene of from 8-16 carbon atoms, alkylene-oxy-alkylene of from 4-14 carbon atoms, alkylene-thio-alkylene of from 4-14 carbon atoms, alkylene-amino-alkylene of from 4-14 carbon atoms, alkylene-alkyl-amino-alkylene of from 5-21 carbon atoms, and alkylene-aryl-amino-alkylene of from 11-23 carbon atoms; and X is selected from the group consisting of chlorine and bromine.

The resulting acid addition salts of the compounds of this invention may be recrystallized from an appropriate solvent such as, for example, water, methanol, ethanol, etc.

It will be appreciated that the compounds of this invention may contain two or more asymmetric carbon atoms in the molecule. The presence of the asymmetric centers gives rise to at least two isolable isomeric forms, of which at least one is a racemic mixture of two optical isomers of the compound.

This invention embraces all of the isomeric forms arising from optically active centers of these compounds. It is intended that the designation of the compounds of this invention, by names and formulae throughout the specification and claims, shall be read to include all isomeric forms and mixtures thereof unless otherwise specified.

Separation of the optically active dextro- and levo-rotary components of ceramic mixtures will be accomplished by methods for resolution well known to the art, such as, for example, the formation of a tartaric acid addition salt using an optically active isomer, such as dextro-tartaric acid. It will be observed that separation of the variously soluble isomeric forms, as well as resolution of the optical isomers themselves, may be effected upon either the methoxy intermediates or upon the hydroxy end products with

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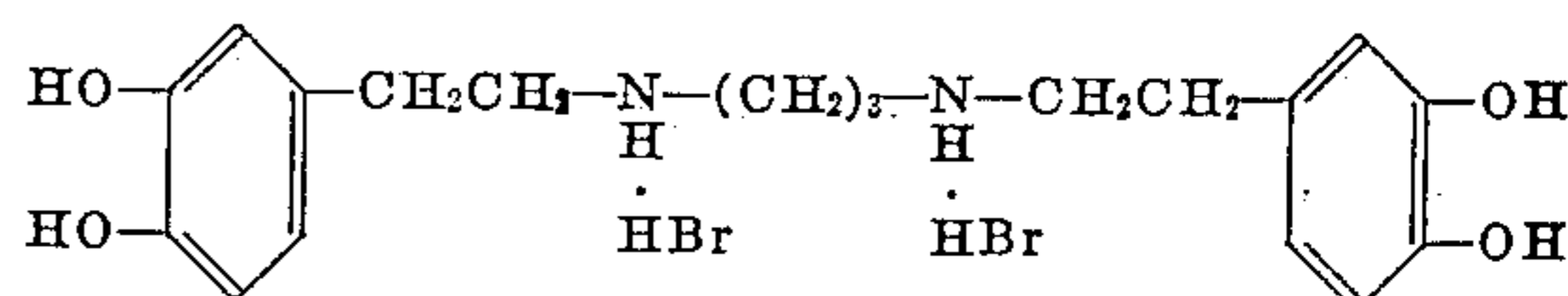
equal practicability. If one of the separated and purified optical isomers or isomeric forms of the methoxy intermediate is subjected to demethylation, the corresponding isomeric form of the hydroxy end product is obtained.

As more specifically illustrative of the compounds of this invention, as well as the method

of their preparation, will be the following specific examples:

Example 1

1,3-bis-(3,4-dihydroxyphenethylamino)-propane dihydrobromide



METHOD A

Step 1.—A solution of 40 g. of 3,4-dimethoxyphenethylamine and 10 g. of trimethylene dibromide in 100 cc. of ethyl alcohol was heated on a steam bath until all the alcohol evaporated. After heating for one additional hour, the residue was dissolved in a small volume of water and made acid with excess 48% hydrobromic acid. After standing overnight in the cold, the product was removed by filtration, washed with water and dried. Recrystallization from water gave 1,3-bis-(3,4-dimethoxyphenethylamino)-propane dihydrobromide, M. P., 250-253° C.

Step 2.—To 10 g. of the product obtained above was added 40 cc. of 48% hydrobromic acid and 0.5 cc. of 50% hypophosphorous acid. The resulting solution was heated at reflux until evolution of methylbromide ceased and the vapor temperature reached 120° C. Removal of the excess acid by distillation in vacuo and recrystallization of the product from water yielded 1,3-bis-(3,4-dihydroxyphenethylamino)-propane dihydrobromide, M. P., 206-207° C.

METHOD B

An alternate method of preparation of 1,3-bis-(3,4-dihydroxyphenethylamino)-propane dihydrobromide is as follows:

Step 1.—A mixture of 44 g. of 1,1,3,3-tetraethoxypropane and 100 cc. of 6 N. hydrochloric acid was warmed at 40° C. for forty minutes. The resulting yellow solution was saturated with sodium chloride and repeatedly extracted with portions of ether. The combined ether solutions were washed with water, saturated with sodium chloride, and then dried over anhydrous po-

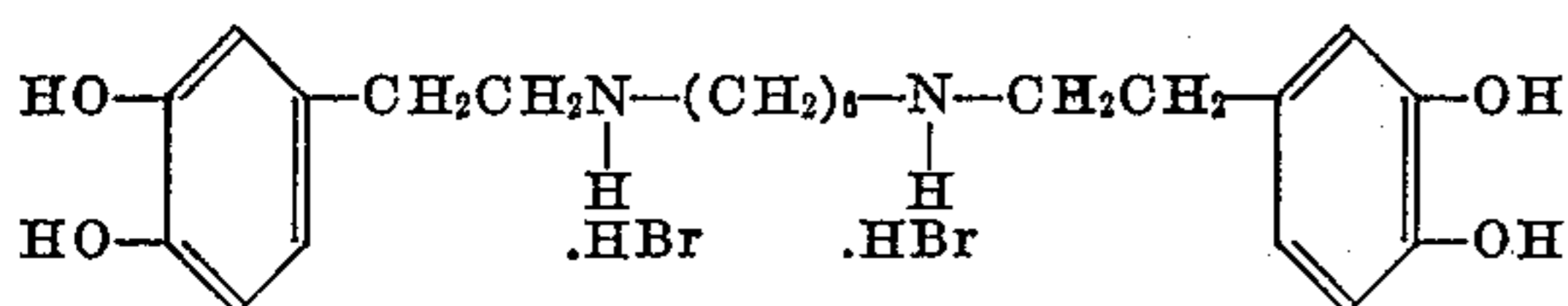
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tassium carbonate. Removal of the drying agent by filtration and the ether by evaporation gave a red oil. The oil and 36.2 g. of 3,4-dimethoxyphenethylamine were dissolved in alcohol and hydrogenated at 50° C. and 50 p. s. i. using Raney nickel catalyst. Removal of the catalyst and distillation in vacuo of the solvent yielded an oil which was treated with excess 48% hydrobromic acid. Crystalline 1,3-bis-(dimethoxyphenethylamino)-propane dihydrobromide was collected by filtration and washed with alcohol and ether; M. P. 256-259° C.

Step 2.—Demethylation of this intermediate was accomplished following the directions of Step 2, Method A, to yield 1,3-bis-(3,4-dihydroxyphenethylamino)-propane dihydrobromide, M. P. 206-207° C.

EXAMPLE 2

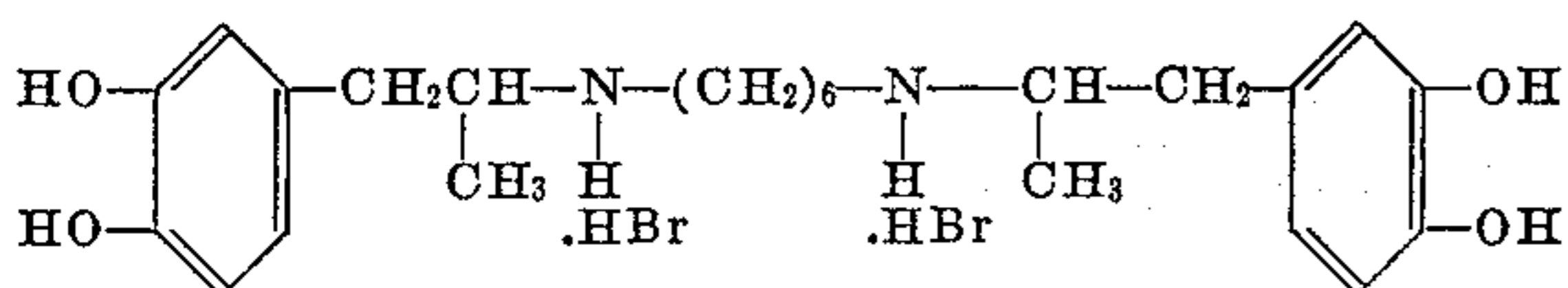
1,6-bis-(3,4-dihydroxyphenethylamino)-hexane dihydrobromide



A mixture of 4.0 g. of 1,6-bis-(3,4-dimethoxyphenethylamino)-hexane dihydrobromide, prepared by standard procedure described in Example 1, and 15 cc. of 48% hydrobromic acid containing 1 cc. of 50% hypophosphorous acid was boiled gently for three hours. Removal of the excess acid and recrystallization of the product from water yielded 1,6-bis-(3,4-hydroxyphenethylamino)-dihydrobromide, M. P. 272-273° C.

EXAMPLE 3

1,6-bis-[β-(3,4-dihydroxyphenyl)-isopropylamino]-hexane dihydrobromide

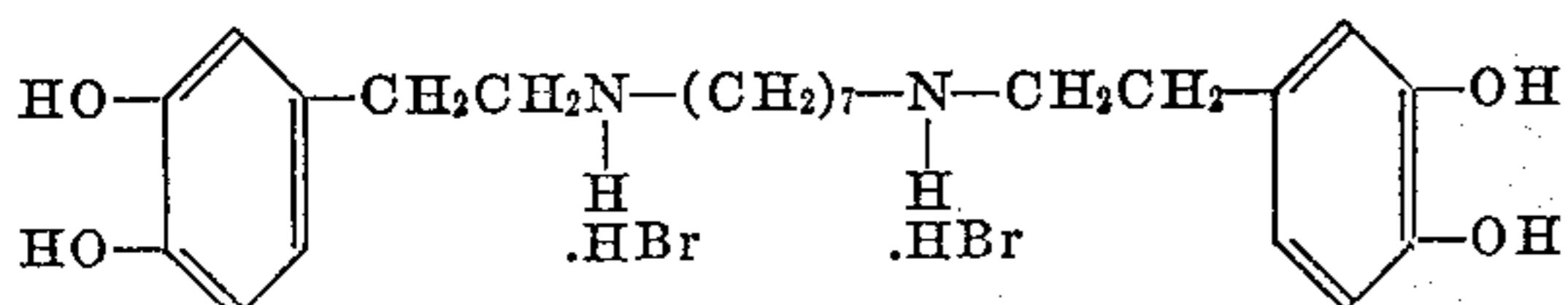


A mixture of 39 g. of 3,4-dimethoxyphenylisopropylamine and 12.2 g. of hexamethylenedibromide was warmed on a steam bath for two hours. The glass-like solid obtained upon cooling was treated with 100 cc. of 10% sodium hydroxide and the resultant oil was extracted into ether. The ether solution was dried over MgSO₄ and evaporated. Distillation in vacuo of the residue gave a primary amine, B. P. 116-117°/0.5 mm. The undistilled residue was dissolved in 75 cc. of alcohol, acidified with ethereal hydrogen chloride, diluted with ether and cooled to give 1,6-[β-(3,4-dimethoxyphenyl)-isopropylaminol]-hexane dihydrochloride, M. P. 220-228° C. Treating this material with cold methanol gave a partial separation of the two isomeric forms; M. P. 256-257 and M. P. 226-227° C.

Demethylation of a mixture of both forms of the bis-methoxy intermediate by the procedure described in Example 1, gave 1,6-bis-[β-(3,4-dihydroxyphenyl)-isopropylamino]-hexane dihydrobromide, M. P. 264-267° C. (dec.)

EXAMPLE 4

1,7-bis-(3,4-dihydroxyphenethylamino)-heptane dihydrobromide



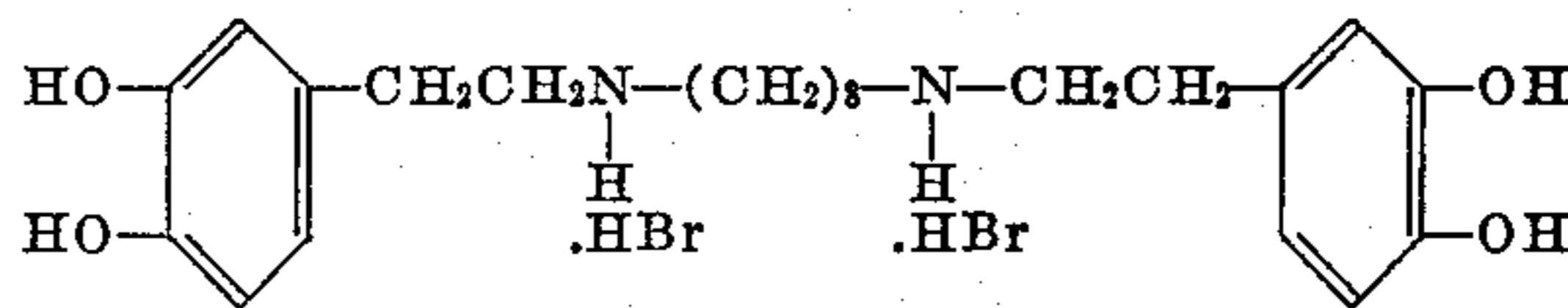
In this preparation, Method A of Example 1 was

6

followed, except that 1,7-dibromoheptane was used in place of 1,3-dibromopropane. Demethylation of the intermediate yielded 1,7-bis-(3,4-dihydroxyphenethylamino)-heptane dihydrobromide; M. P. 198-199° C. (dec.) after recrystallization from water and ethanol.

EXAMPLE 5

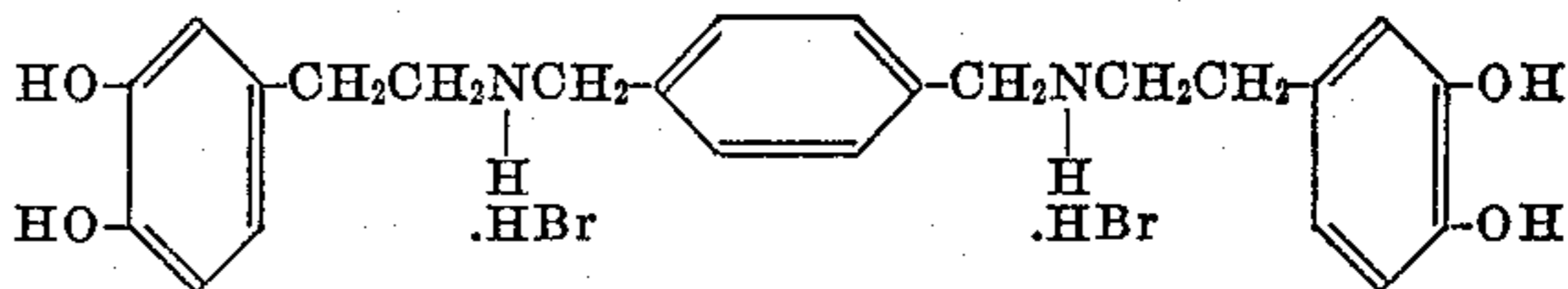
1,8-bis-(3,4-dihydroxyphenethylamino)-octane dihydrobromide



In this preparation, Method A of Example 1 was followed except that 1,8-dibromooctane was used in place of 1,3-dibromopropane. Demethylation of the intermediate yielded 1,8-bis-(3,4-dihydroxyphenethylamino)-octane dihydrobromide; M. P. 253-254° C. after recrystallization from water.

EXAMPLE 6

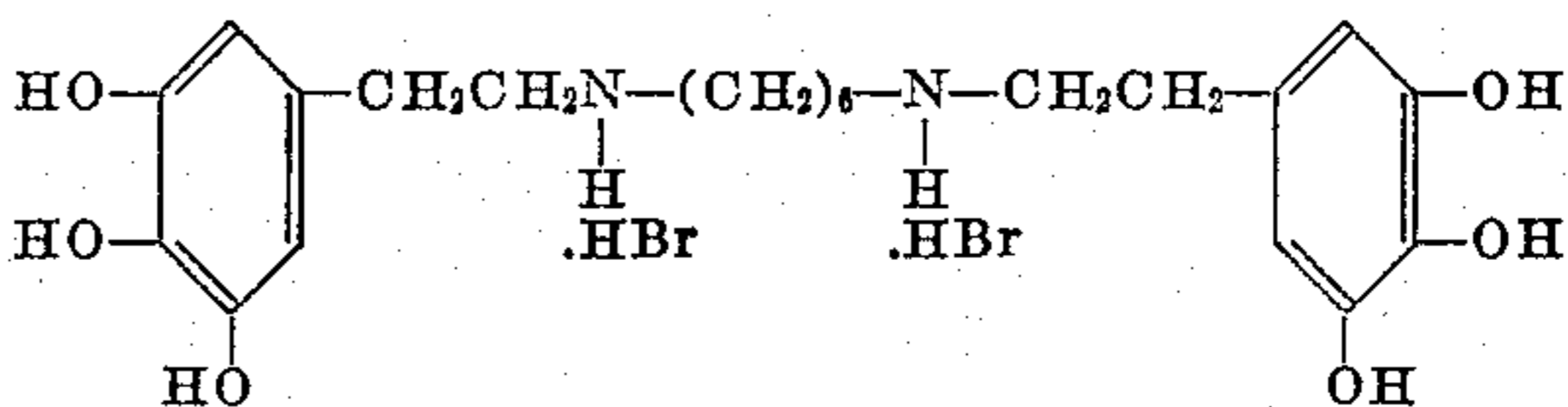
1,4-bis-(3,4-dihydroxyphenethylaminomethyl)-benzene dihydrobromide



Sixteen grams of 3,4-dimethoxyphenethylamine was added with stirring to 5 g. of α,α'-dibromo-p-xylene in 50 cc. of alcohol and the mixture was heated on a steam bath to evaporate the solvent. The residue was diluted with 100 cc. of water and acidified with excess 48% hydrobromic acid. The very insoluble salt of the intermediate dimethoxy compound was collected by filtration, washed and dried. This material was suspended in 100 cc. of 48% hydrobromic acid containing 0.5 cc. of 50% hypophosphorous acid and was boiled until the evolution of methyl bromide ceased. The reaction mixture was cooled and the product, 1,4-bis-(3,4-dihydroxyphenethylaminomethyl)-benzene dihydrobromide was separated by filtration. On recrystallization from water, the product gave a melting point of 295-298° C.

EXAMPLE 7

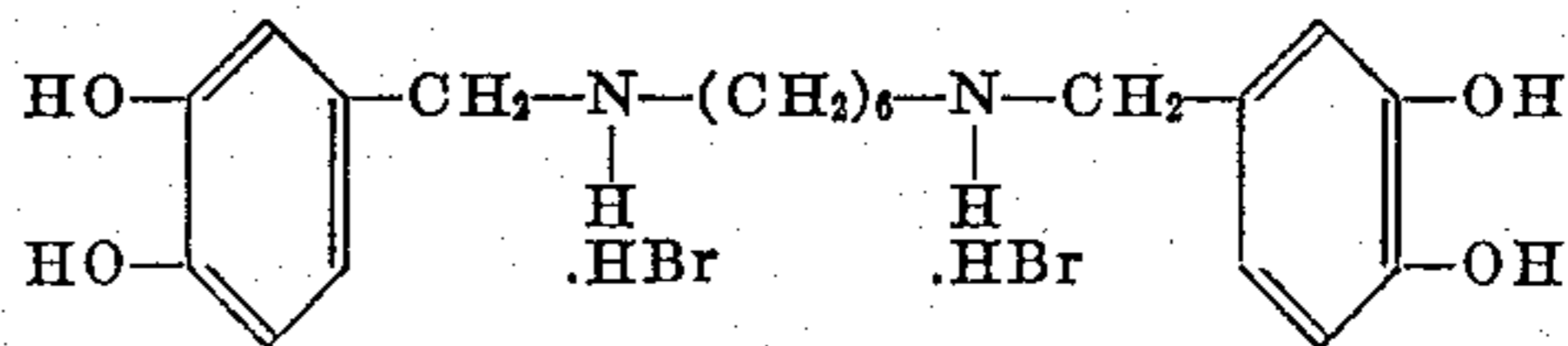
1,6-bis-(3,4,5-trihydroxyphenethylamino)-hexane dihydrobromide



In this preparation, the directions of Example 2 are followed except that 3,4,5-trimethoxyphenethylamine is used in place of the 3,4-dimethoxyphenethylamine. Demethylation of the bis-methoxy intermediate by the method described in Example 1 gave 1,6-bis-(3,4,5-trihydroxyphenethylamino)-hexane dihydrobromide.

EXAMPLE 8

1,6-bis-(3,4-dihydroxybenzylamino)-hexane dihydrobromide



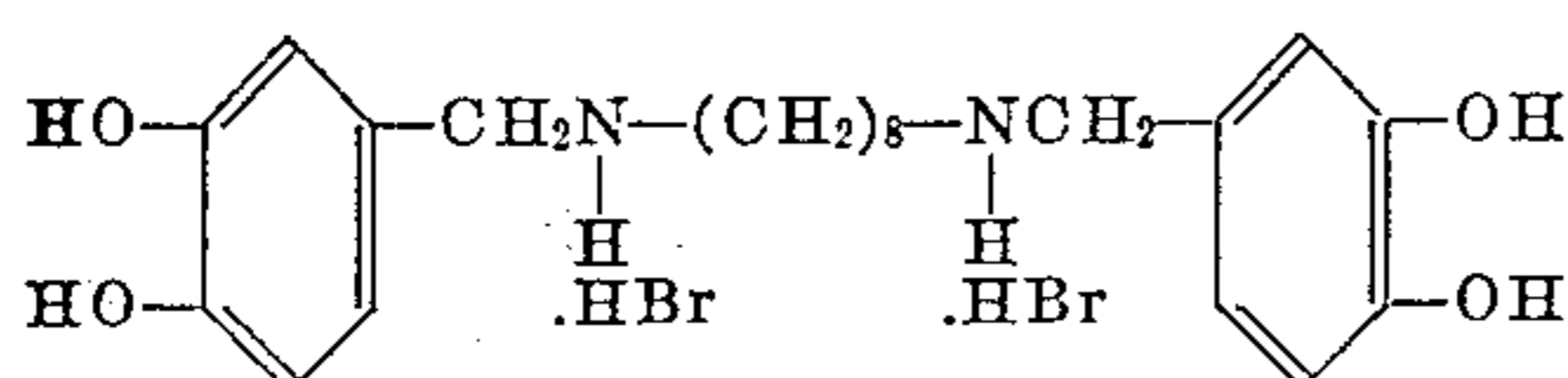
A mixture of 3,4-dimethoxybenzylamine and 1,6-dibromohexane was treated according to the

7

procedure of Method A, Example 1, to give 1,6-bis-(3,4-dimethoxybenzylamino)-hexane. Demethylation of this material by the method described in Example 1 and recrystallization of the product from methanol-water gave 1,6-bis-(3,4-dihydroxybenzylamino)-hexane dihydrobromide, M. P. 234-235° C. (dec.).

EXAMPLE 9

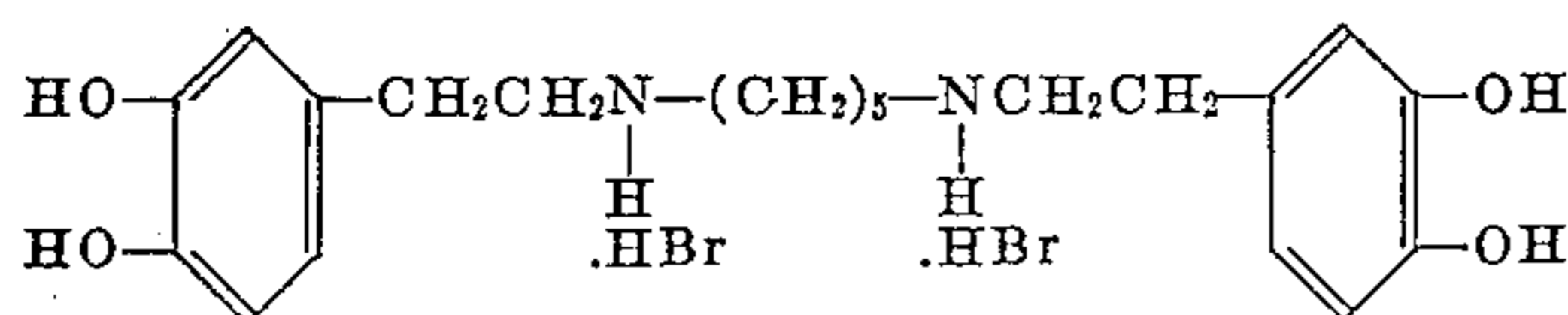
1,8-bis-(3,4-dihydroxybenzylamino)-octane dihydrobromide



In this preparation, the procedure set forth in Example 8 is followed except that 1,8-dibromooctane is used in place of 1,6-dibromohexane. The desired product was recrystallized from water; M. P. 239-240° C.

EXAMPLE 10

1,5-bis-(3,4-dihydroxyphenethylamino)-pentane dihydrobromide

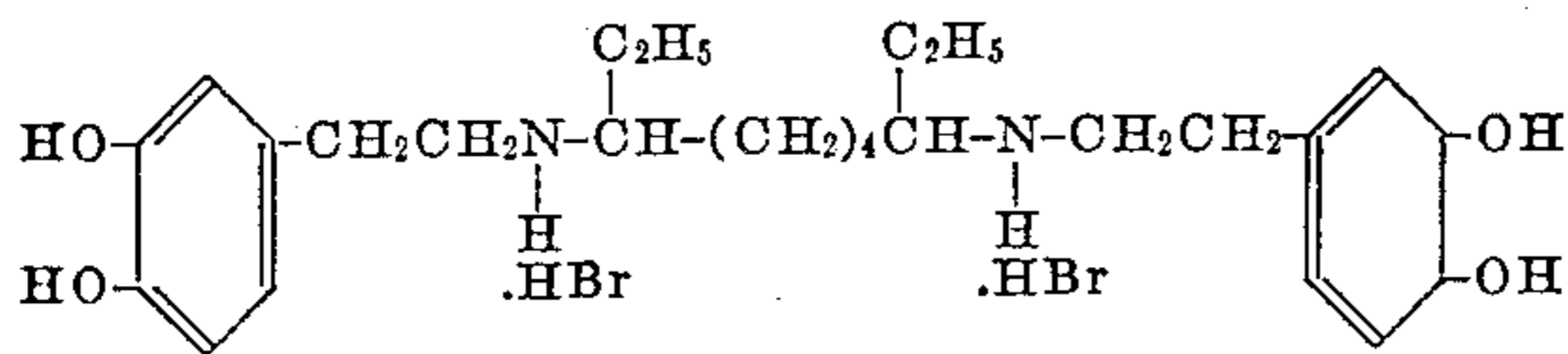


22.8 g. of N,N-bis-(3,4-dimethoxyphenethyl)-glutaramide, prepared by the method of Hahn and Gudjons, Ber. 71, 2186 (1938), was dissolved in 200 cc. of tetrahydrofuran and the solution was added slowly with stirring to a mixture of 4.56 g. of lithium aluminum hydride and 112 c. of dry distilled tetrahydrofuran, which had been stirred at 40-50° for one hour. After this initial addition was completed, another 1.5 g. lithium aluminum hydride was added and the mixture was refluxed with stirring for two hours. The mixture was cooled in ice while 12 cc. of water was added cautiously. Impurities were removed by filtration and the filtrate was dried over anhydrous MgSO₄, which was also removed by filtration. The filtrate was acidified with excess ethereal hydrogen chloride. The white solid was filtered off and recrystallized from alcohol to yield 1,5-bis-(3,4-dimethoxyphenethylamino)-pentane dihydrochloride, M. P. 251-254° C.

Demethylation of this material by procedures described yielded 1,5-bis-(3,4-dihydroxyphenethylamino)-pentane dihydrobromide, M. P. 218-220° C.

EXAMPLE 11

1,6-bis-(3,4-dihydroxyphenethylamino)-1,6-diethyl hexane dihydrobromide

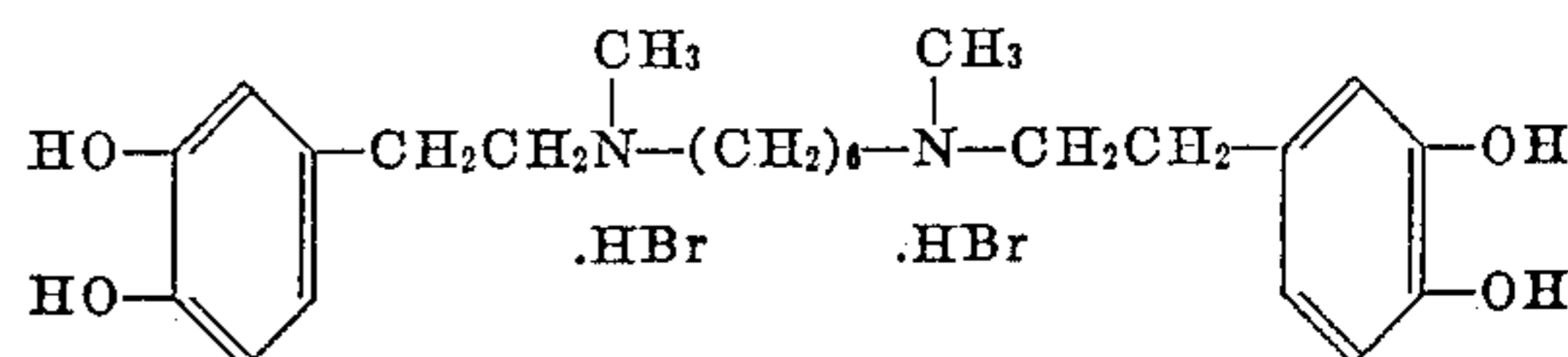


A mixture of 3,4-dimethoxyphenethylamine and 1,6-diethyl-1,6-dibromohexane was treated according to the procedure of Method A, Example 1. Demethylation by the procedure described in Example 1, and recrystallization produced the desired product, 1,6-bis-(3,4-dihydroxyphenethylamino)-1,6-diethylhexane dihydrobromide.

8

EXAMPLE 12

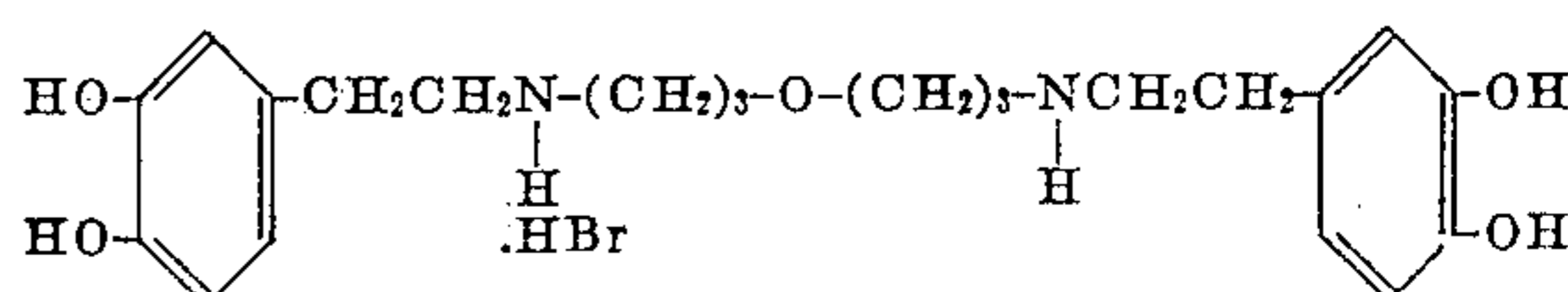
1,6-bis-(N-methyl-3,4-dihydroxyphenethylamino)-hexane dihydrobromide



1,6-bis-(3,4-methoxyphenethylamino)-hexane dihydrochloride was prepared using the procedure of Example 1 except that an equimolar quantity of N-methyl-3,4-dimethoxyphenethylamine was used in place of 3,4-dimethoxyphenethylamine. Demethylation by the method described in Example 1 and recrystallization of the final product from water yielded 1,6-bis-(N-methyl-3,4-dihydroxyphenethylamino)-hexane dihydrobromide.

EXAMPLE 13

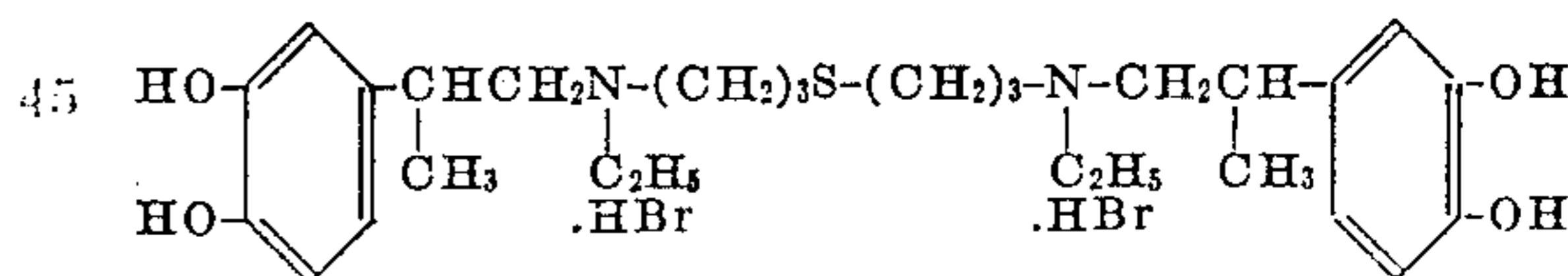
1,7-bis-[β-(3,4-dihydroxyphenethyl)amino]-4-oxaheptane dihydrobromide



An excess of 3,4-dibenzyloxyphenethylamine was added to di-γ-chloropropylether and the mixture was heated at 100° C. for two hours. The mixture was then treated with a slight excess of hot 10% hydrochloric acid and cooled. The resulting dihydrochloride salt of the benzyloxy intermediate was reductively debenzylated using palladium-charcoal catalyst. Removal of the aqueous solvent yielded 1,7-bis-[β-(3,4-dihydroxyphenethyl)amino]-4-oxaheptane dihydrobromide.

EXAMPLE 14

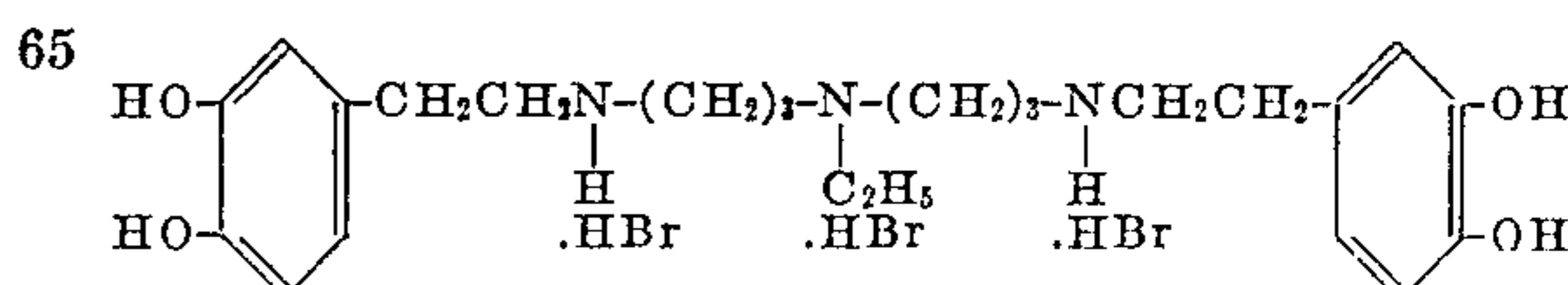
1,7-bis-[N-ethyl-β-methyl-β-(3,4-dihydroxyphenyl)-ethylamino]-4-thiaheptane dihydrobromide



An excess of β-methyl-β-(3,4-dimethoxyphenyl)-ethylamine was added to di-γ-bromopropylsulfide and the mixture was heated at 100° C. for two hours. The mixture was then treated with a slight excess of hot 10% hydrochloric acid and cooled. The resulting dihydrochloride salt of the methoxy intermediate was demethylated using the procedure described in Example 1. Removal of the excess hydrobromic acid yielded 1,7-bis-[N-ethyl-β-methyl-β-(3,4-dihydroxyphenyl)-ethylamino]-4-thiaheptane dihydrobromide.

EXAMPLE 15

N,N-bis-[γ-(3,4-dihydroxyphenethylamino)-propyl]-ethylamine trihydrobromide

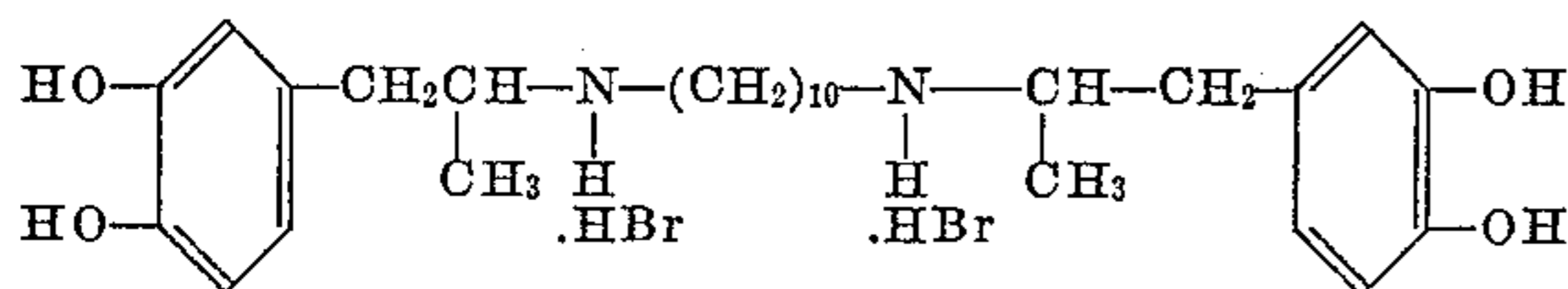


An excess of 3,4-dimethoxyphenethylamine was added to di-(γ-chloropropyl)-ethylamine and the mixture was heated to 100° for two hours. The mixture was then treated with a slight excess of hot 10% hydrochloric acid and cooled. The resulting trihydrochloride salt of the meth-

oxy intermediate was demethylated using the procedure described in Example 1. Removal of the excess hydrobromic acid yielded N,N-bis-[γ -(3,4-dihydroxyphenethylamino)-propyl]-ethylamine trihydrobromide.

EXAMPLE 16

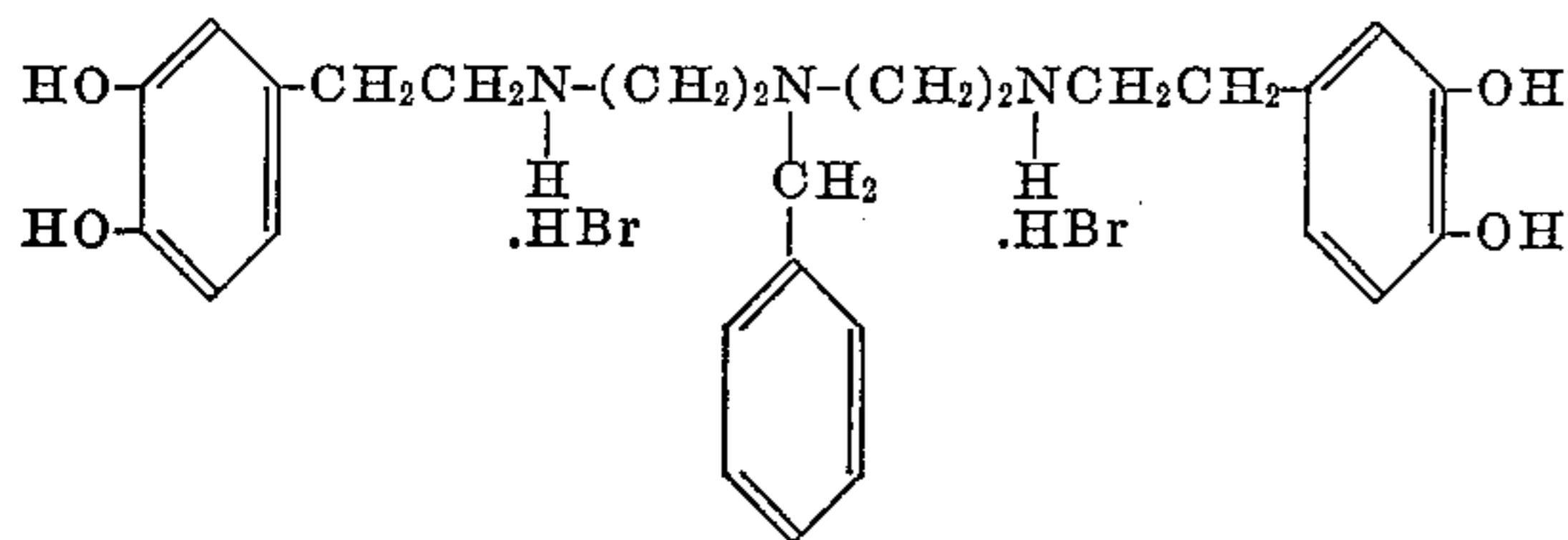
1,10-bis-[β -(3,4-dihydroxyphenylisopropyl)-amino]-decane dihydrobromide



A mixture of 3,4-dimethoxyphenylisopropylamine and 1,10-dibromodecane was treated according to the procedure disclosed in Example 3. Demethylation of the bis-dimethoxy intermediate yielded the desired product, 1,10-bis-[β -(3,4-dihydroxyphenylisopropyl)-amino]-decane dihydrobromide.

EXAMPLE 17

N,N-bis-[β -(3,4-dihydroxyphenethylamino)-ethyl]-benzylamine trihydrobromide



An excess of 3,4-dimethoxyphenethylamine was added to di-(β -chloroethyl)-benzylamine and the mixture was heated to 100° C. for two hours. A slight excess of 10% hydrochloric acid was added and the mixture was cooled. The resulting bis-methoxy intermediate was demethylated according to the procedure described in Example 1, to yield N,N-bis-[β -(3,4-dihydroxyphenethylamino)-ethyl]-benzylamine trihydrobromide.

EXAMPLE 18

1,7-bis-(3,4-dihydroxyphenethylamino)-heptane dihydrochloride

An aqueous solution of 1,7-bis-(3,4-dihydroxyphenethylamino)-heptane dihydrobromide, prepared in Example 4, was treated with a slight excess of sodium bicarbonate solution. The free base, which precipitated from solution and was collected by filtration, was dissolved by heating in 10% hydrochloric acid. On cooling, the dihydrochloride salt precipitated from solution; M. P. 225-229° C. (dec.)

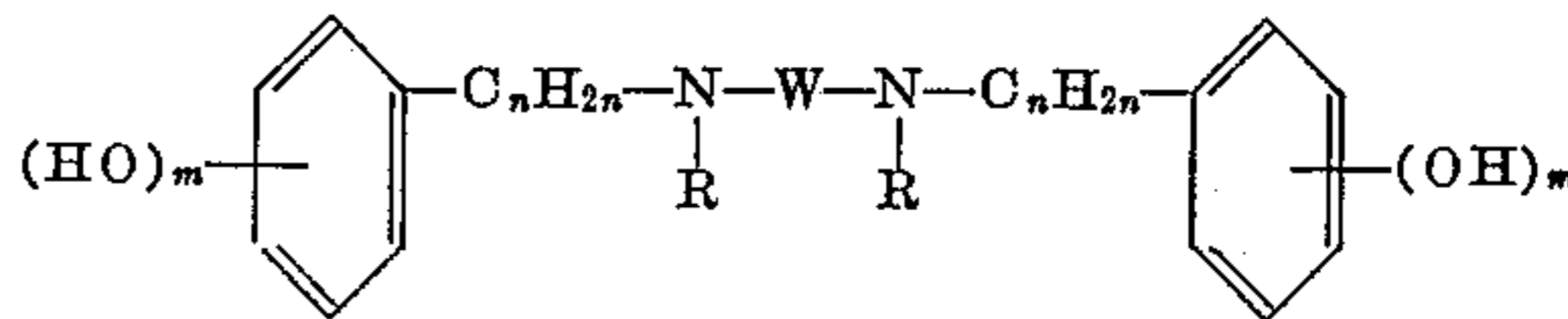
Other inorganic and organic acid addition salts contemplated by this invention are prepared from the various free bases by methods well known to the art, as by neutralizing a free base with a desired inorganic or organic acid in the presence or absence of a solvent.

The bases contemplated by this invention will be formed by carefully interacting the salts contemplated by this invention and herein exhaustively exemplified with one molecular equivalent of a basic reagent such as, for example, sodium bicarbonate, potassium bicarbonate, sodium carbonate or the like, in aqueous solution at room temperature or below and the bases so liberated are separated by filtration or centrifugation. The preparation of free bases and the subsequent preparation of the hydrochloride salt is illustrated in Example 18.

It will be appreciated by those skilled in the art that various modifications may be made within the scope of this invention without departing from the spirit thereof, and the scope of the invention is to be restricted only in accordance with the appended claims.

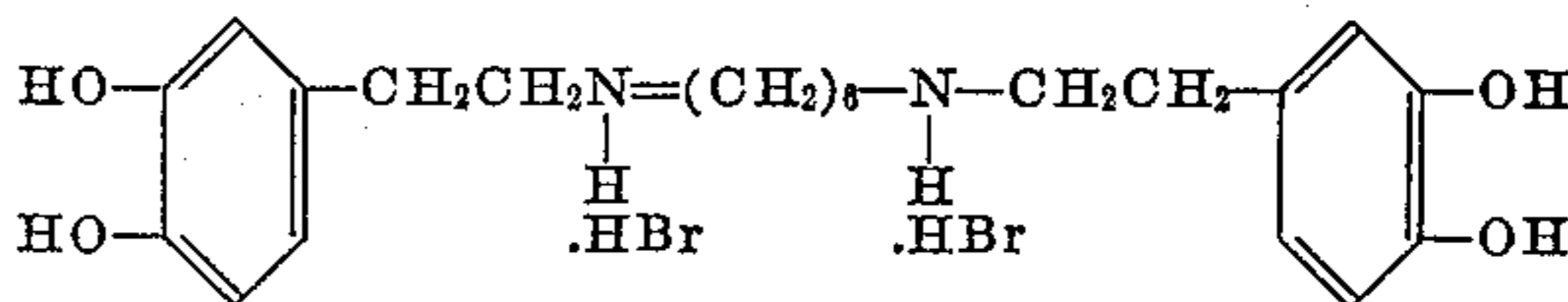
What is claimed is:

1. Compounds selected from the group consisting of a free base and its acid addition salts, said free base having the structure

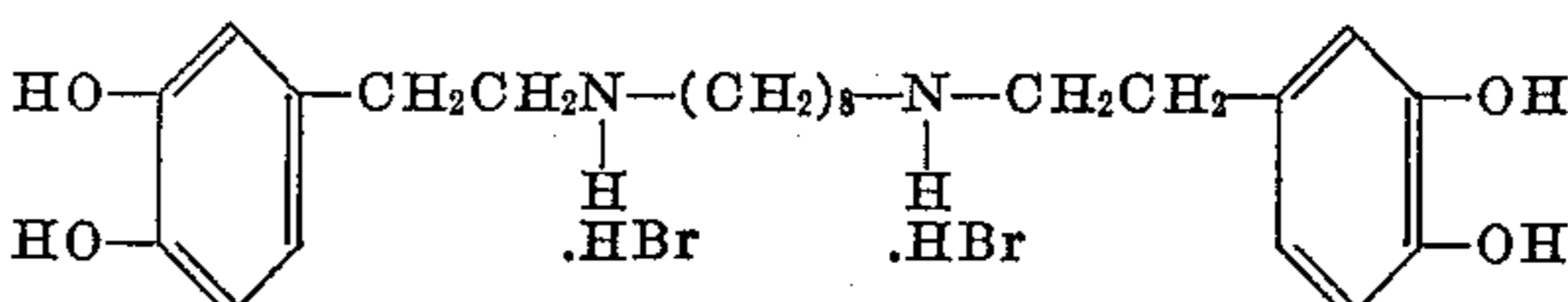


in which m is an integer from the group consisting of 2 and 3; n is an integer from 1 to 6 inclusive; R is selected from the group consisting of hydrogen and lower alkyl; W is a bridging member selected from the group consisting of alkylene having not more than 14 carbon atoms, alkylene-phenylene-alkylene having 8 to 16 carbon atoms, alkylene-oxy-alkylene having 4 to 14 carbon atoms, alkylene-thio-alkylene having 4 to 14 carbon atoms, alkylene-amino-alkylene having 4 to 14 carbon atoms, alkylene-alkylamino-alkylene having 5 to 21 carbon atoms, and alkylene-aralkylamino-alkylene having 11 to 23 carbon atoms.

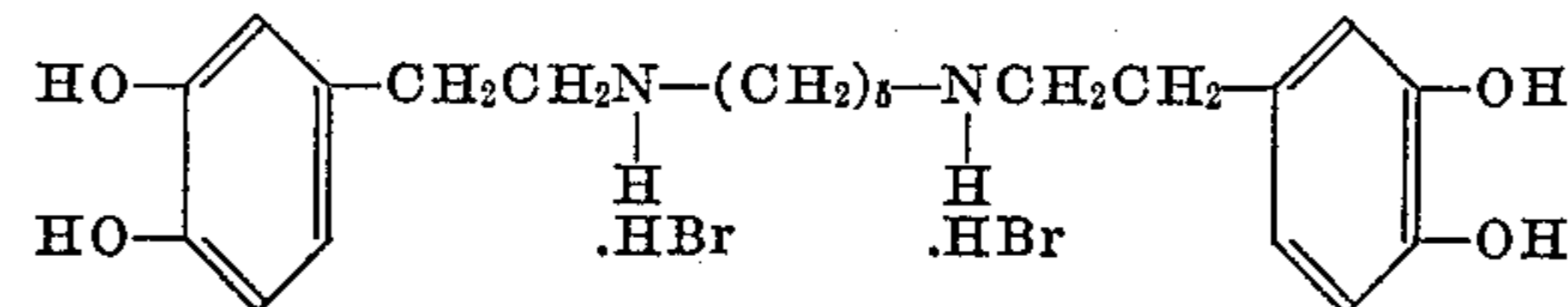
2. The compound having the following formula:



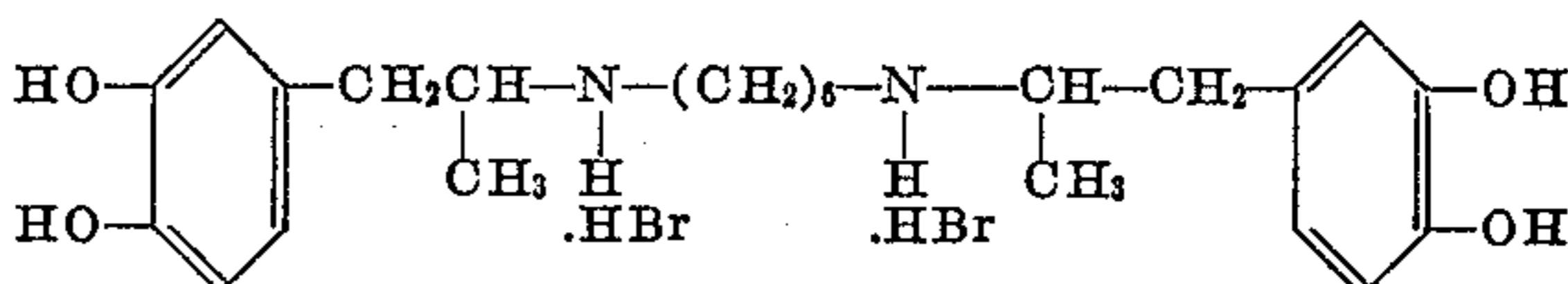
3. The compound having the formula:



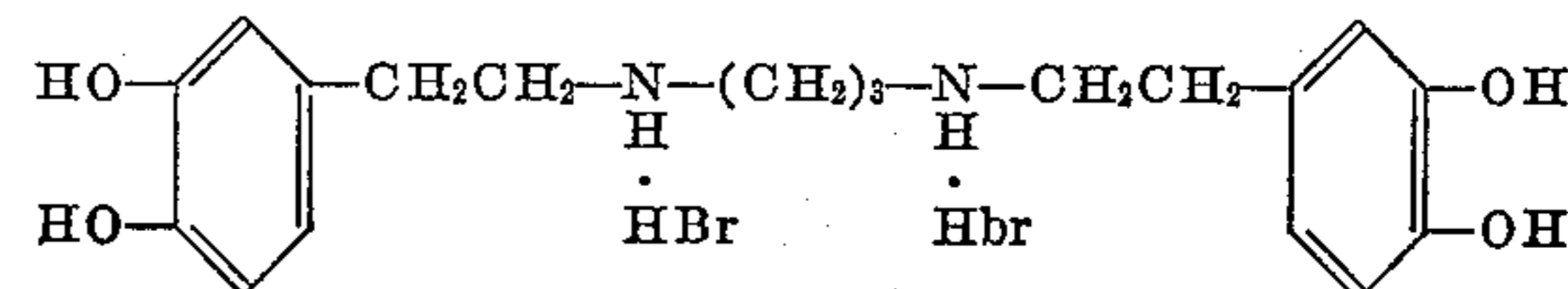
4. The compound having the formula:



5. The compound having the formula:



6. The compound having the formula:



PAUL N. CRAIG.
FRED P. NABENHAUER.

References Cited in the file of this patent

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Number	Name	Date
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FOREIGN PATENTS

Number	Country	Date
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