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DIBENZYL-BIS-AMMONIUM SALTS

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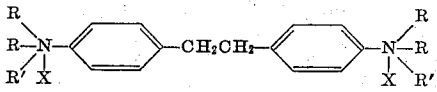
1 Claim. (Cl. 260—567.6)

This invention relates to new aryl quaternary ammonium salts.

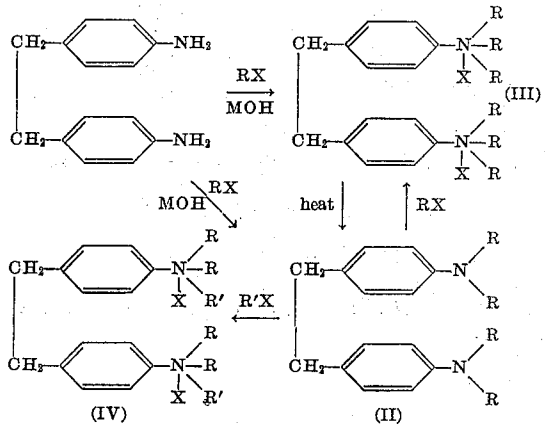
A primary object of the invention is the embodiment of a new group of compounds characterized by a potent curare-like activity and by freedom from undesired side effects such as hypotension, respiratory paralysis, bronchiospasm, salivation, etc.

This object is realized, according to the present invention, by a new group of aryl quaternary amines which correspond to the formula



wherein R stands for a lower alkyl group, such as methyl, ethyl, propyl, butyl, etc., R′ stands for a lower alkyl group (which may be the same as or different from the lower alkyl group represented by R) or for an aralkyl radical, such as benzyl, alkylated benzyl, alkoxylated benzyl, halogenated benzyl, etc., and X stands for a halogen atom as for example, a chlorine, bromine or iodine atom. These compounds fulfill the aforementioned desiderata in that, in addition to a high curare-like activity, they do not cause the aforesaid undesired side effects. The compounds are thus useful therapeutically, and may be administered intramuscularly, intravenously or orally. The activity by oral administration is of great importance for the treatment of Parkinson's disease to reduce muscle tremors.

The compounds of the invention are prepared by refluxing for example a 4,4′-diamino-dibenzyl in solution with an excess of an alkylating agent such as an alkyl halide or a dialkyl sulfate together with an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, according—in the case of 4,4′-diamino-dibenzyl itself— to the following reaction scheme:



wherein R, R′ and X have the previously indicated significances and M stands for an alkali metal.

When the alkylating agent is methyl iodide, the product, dibenzyl-4,4′-bis-trimethylammonium iodide crystallizes from the reaction mixture. When the alkylating agent is an alkyl halide containing two or more carbon atoms, it is possible to stop the alkylating process at the tertiary amine stage (II) and then to complete quaternation in an additional step wherein if desired another alkylating agent is employed.

The quaternary ammonium compounds (III), when subjected to heat, lose alkyl halide to form the bis-tertiary amino dibenzyl derivative which then may be quaternized using the same or a different alkylating agent or an aralkylating agent to produce the quaternary compounds (IV).

The iodide salt may be converted to the bromide or the chloride salt by treating the quaternary iodide with silver bromide or silver chloride respectively.

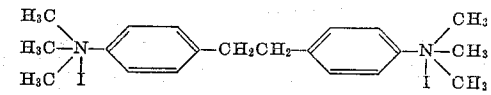
Examples of suitable alkyl and aralkyl halides are methyl iodide, ethyl iodide, propyl iodide, benzyl bromide, ethyl bromide, ethyl chloride, p-methoxybenzyl bromide, p-methylbenzyl bromide and the like.

Alternatively, 4,4′-diamino-dibenzyl is alkylated by heating under pressure with an alcohol at a temperature of 200° C. In this way diamino-dibenzyl may be alkylated with ethyl alcohol, propyl alcohol, and the like.

The following examples set forth representative exemplary embodiments of the invention, and these examples are intended to be illustrative and not limitative. In these examples, parts by weight bear the same relation as to parts by volume as does the kilogram to the liter. Temperatures are expressed in degrees centigrade. Percentages are by weight. All melting points are uncorrected.

Example 1

25 parts by weight of 4,4′-diamino-dibenzyl are refluxed in 300 parts by volume ethanol with 33 parts by weight of sodium hydroxide and 85 parts by volume of methyl iodide. After six hours of refluxing, during which time the crystalline product slowly separates, the reaction is complete. The crystalline material is separated and, by recrystallization from hot water, yields dibenzyl-4,4′-bis-(trimethylammonium iodide)



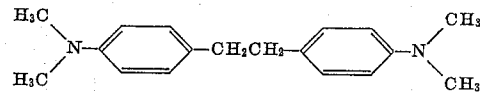
which melts at 235–240° (with decomposition).

Example 2

1 part by weight of dibenzyl-4,4′-(trimethylammonium iodide) is stirred with wet freshly-prepared silver chloride (prepared from silver nitrate with hydrochloric acid) for ½ hour. The silver halides are removed and the aqueous solution concentrated to dryness in vacuo. The crystalline residue of dibenzyl-4,4′-bis-(trimethylammonium chloride) is recrystallized from ethanol whereupon it melts at 235° (with decomposition).

Example 3

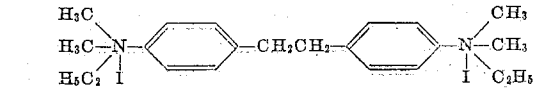
10 parts by weight of dibenzyl-4,4′-(trimethylammonium iodide) are heated at 250° under 15 mm. pressure for ½ hour. The residue is extracted with benzene, and the benzene extracted with aqueous hydrochloric acid. On making the latter extract alkaline with ammonia, 4,4′-bis-(dimethylamino)-dibenzyl separates. The product, which corresponds to the formula



melts at 152–156°, after crystallization from ethanol. By reaction with methyl iodide in alcohol solution, this amine can be converted into dibenzyl-4,4′-bis-(trimethylammonium iodide).

Example 4

5 parts of 4,4'-bis-(dimethylamino)-dibenzyl are refluxed overnight with 6 parts by volume of ethyl iodide in 50 parts by volume of ethanol-benzene mixture (10:1). Ethyl acetate is added to complete the crystallization of the quaternary salt. It is recrystallized from 95% ethanol, yielding dibenzyl-4,4'-bis-(dimethylethylammonium iodide)



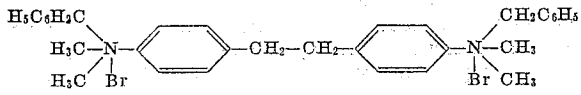
which melts at 213–217° (with decomposition).

Example 5

By substituting 6 parts by volume of propyl iodide for the ethyl iodide employed in Example 4 and otherwise proceeding as described in the latter, there is obtained dibenzyl - 4,4' - bis - (dimethylpropylammonium iodide) which melts at 193–197° (with decomposition).

Example 6

By substituting 4.4 parts by volume of benzyl bromide for the ethyl iodide employed in Example 4 and otherwise proceeding as described in the latter, there is obtained dibenzyl-4,4'-bis-(benzyldimethylammonium bromide)



which melts at 150–153° (with decomposition).

Example 7

20 parts by weight of 4,4'-diamino-dibenzyl are refluxed for 12 hours with 31 parts by volume of ethyl iodide and 15.2 parts by weight of sodium hydroxide in 300 parts by volume of ethanol. The solution is concentrated to a small volume, the formed sodium iodide is filtered off, and water added to the filtrate. An oil precipitates, which crystallizes on standing. It is recrystallized from methanol to yield 4,4'-bis-(diethylamino)-dibenzyl, melting at 80–83°. Reaction with methyl iodide in the manner hereinbefore described yields dibenzyl-4,4'-bis-(diethylmethylammonium iodide) which melts at 225–230° (with decomposition); and reaction with benzyl bromide yields dibenzyl-4,4'-bis-(benzyldiethylammonium bromide) which melts at 235–241° (with decomposition).

Example 8

20 parts by weight of 4,4'-diamino-dibenzyl are refluxed for 12 hours with 20 parts by weight of sodium hydroxide and 60 parts by volume of ethyl iodide in 300 parts by volume of ethanol. The mixture is concentrated to a small volume, the sodium iodide which crystallizes is removed by filtration, and water is added to the filtrate. The gummy material which precipitates is shaken with an excess of freshly-prepared silver chloride (about 100 parts by weight) in about 500 parts by volume of water. The silver salts are filtered off, and the aqueous portion evaporated to dryness in vacuo. The solid residue is extracted with a minimum quantity of hot ethyl alcohol, and any sodium chloride which remains undissolved is filtered off. Ethyl acetate is added to the filtrate until turbidity sets in and, on cooling, crystalline dibenzyl-4,4'-bis-(triethylammonium chloride), melting at 216–221° with decomposition, is obtained.

Example 9

5 parts by weight of 4,4'-bis-(dimethylamino)-dibenzyl and 6.9 parts by weight of p-methylbenzyl bromide are refluxed for ½ hour in 20 parts by volume of acetone. The oil which separates is recrystallized from ethanol-ethyl acetate to yield dibenzyl-4,4'-bis-(dimethyl-p-methylbenzyl-ammonium bromide); melting point 194–198° (decomposition).

Example 10

5 parts by weight of 4,4'-bis-(dimethylamino)-dibenzyl and 8.1 parts by weight of p-nitrobenzyl bromide are dissolved in 20 parts by volume of dry acetone and allowed to stand overnight at room temperature (e. g. 20 to 30°). An oil gradually precipitates which is recrystallized from ethanol-ethyl acetate to yield dibenzyl-4,4' - bis - (dimethyl - p - nitrobenzyl - ammonium bromide); melting point 140–143° (decomposition).

Example 11

5 parts by weight of 4,4'-bis-(dimethylamino)-dibenzyl and 6 parts by weight of p-chlorobenzyl chloride are refluxed for 5 minutes in 25 parts by volume of ethanol. Ethyl acetate is added until a cloudiness appears. The small amount of gum which precipitates is separated and on further standing the desired crystalline quaternary compound, dibenzyl - 4,4' - bis - (dimethyl - p - chlorobenzyl ammonium chloride) is obtained; melting point 123–126°.

Proceeding similarly using 5.05 parts by volume of m-methylbenzyl bromide instead of the p-chlorobenzyl chloride, there is obtained dibenzyl-4,4'-bis-(dimethyl-m-methylbenzyl ammonium bromide); melting point 143–146°.

Example 12

2 parts by weight of 4,4'-bis-(dimethylamino)-dibenzyl and 3 parts by weight of p-methoxybenzyl bromide are refluxed for 5 minutes in 25 parts by volume of ethanol. Ethyl acetate is added to precipitate the oily product which is redissolved in ethanol and reprecipitated with ethyl acetate to free the preparation from unreacted starting material. The oil is dried in vacuo to yield dibenzyl-4,4'-bis-(dimethyl-p-methoxybenzyl-ammonium bromide) in a resinous state. By dissolving in water, a solution is obtained which is suitable for therapeutic purposes. By dissolving in water and adding an aqueous solution of picrylsulfonic acid, there is obtained the dipicrylsulfonate salt; melting point 170° (decomposition).

Having thus disclosed the invention, what is claimed is:

Dibenzyl-4,4'-bis-(triethylammonium chloride).

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