Patented Nov. 7, 1950 2,528,939

UNITED STATES PATENT OFFICE

2,528,939

PYRROLIDYLETHYL CARBAZOLE COMPOUNDS

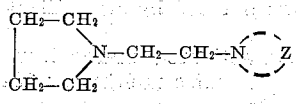
John B. Wright, Kalamazoo, Mich., assignor to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

No Drawing. Application January 21, 1949, Serial No. 72,059

6 Claims. (Cl. 260—313)

1

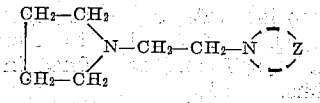
This invention relates to antihistaminics and is more particularly concerned with (1) 1-[beta-(1-pyrrolidyl)-ethyl]-carbazole compounds having the formula:



wherein Z is the remainder of a radical selected from the group consisting of (*a*) the carbazole radical, and (*b*) hydrocarbazole radicals having up to and including four double bonds of the carbazole radical saturated with hydrogen, and (2) acid addition and quaternary ammonium salts thereof.

It is an object of the present invention to provide a novel group of compounds possessing utility as therapeutics for the treatment of allergic manifestations. A further object of the present invention is to provide therapeutically-active antihistamine compounds which are easily synthesized from readily available materials. Another object of the present invention is to provide novel antihistaminics containing the pyrrolidyl nucleus. The compounds are additionally useful as intermediates in the preparation of more complex organic molecules. Other objects will become apparent hereinafter.

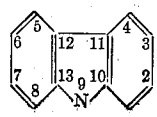
The foregoing and additional objects are accomplished by the provision of compounds of the formula:



wherein Z is the remainder of a radical selected from the group consisting of carbazole and hydrogenated carbazole radicals, e. g., those mentioned below, and acid addition and quaternary ammonium salts thereof. These novel compounds have been found to counteract histamine-induced spasm of smooth muscle tissue, and are therefore useful in the treatment of various allergic manifestations, such as hay fever. The radicals comprising the



group of the present invention are the carbazole radical,



2

and hydrogenated derivatives of the carbazole radical wherein from one to four double bonds of the carbazole radical are saturated with hydrogen.

The double bonds of the carbazole radical which may be saturated by hydrogen are in the 1,2, the 1,2,3,4, the 1,2,3,4,10,11, the 1,2,3,4,5,6, the 1,2,3,4,5,6,7,8, or the 1,2,3,4,5,6,10,11 positions, depending upon the particular N-sodium dihydro-, tetrahydro-, hexahydro- or octahydrocarbazole derivative employed as starting material. These carbazole or hydrocarbazole radicals are joined through the nitrogen atom to the beta-carbon atom of the (1-pyrrolidyl)-ethyl radical to make up the compounds of the present invention, as illustrated by the above structural formula. The compounds of the present invention, then, are, for example:

9-[beta-(1-pyrrolidyl)-ethyl]-carbazole,
9-[beta-(1-pyrrolidyl)-ethyl]-1,2-dihydrocarbazole,
9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole,
9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4,5,6-hexahydrocarbazole,
9-[beta-(1-pyrrolodyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole,
9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4,5,6,7,8-octahydrocarbazole,
9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4,5,6,10,11-octahydrocarbazole,

and acid addition and quaternary ammonium salts thereof, depending upon the particular N-sodium carbazole compound reacted with the beta-(1-pyrrolidyl)-ethyl chloride in the condensation step, as more fully described in the following.

The free base of the present invention may be conveniently prepared by condensing the N-sodium salt of the selected carbazole compound, e. g., carbazole, 1,2-dihydrocarbazole, 1,2,3,4-tetrahydrocarbazole, or 1,2,3,4,10,11-hexahydrocarbazole, with beta-(1-pyrrolidyl)-ethyl chloride in an aromatic hydrocarbon solvent, e. g., toluene or xylene. The sodium salt of the carbazole may be formed according to known procedure, as by heating the selected carbazole with sodamide at about 130 degrees centigrade using xylene as a solvent, or by heating the selected carbazole with metallic sodium at a temperature of 180–200 degrees centrigrade. The condensation step may be conveniently effected by adding the beta-(1-pyrrolidyl)-ethyl chloride or its hydrochloride to a suspension of the selected N-

sodium carbazole compound and heating the mixture for several hours at reflux temperature. The sodium chloride, formed as a by-product, is separated and washed to remove any adhering condensation product, the product extracted with acid, the acid extract neutralized, the free base extracted with ether, and fractionally distilled. When the reaction product is solid, the distillation step is omitted and the product purified by crystallization. This procedure represents a preferred method for the preparation of the compounds of the present invention, but other solvents and reaction conditions for the condensation of alkyl halogen compounds with an amino nitrogen which are known to the art may also be used and will be found satisfactory.

The quaternary ammonium salts of the present invention which are, for some applications, even more desirable than the free base as therapeutic agents, may be prepared in any convenient manner known in the art, as by mixing the free base with an acid in stoichiometric proportions, either in the presence of an organic solvent in which the salt is insoluble so that precipitation occurs upon formation thereof, or by merely admixing solutions of the acid and amine and evaporating to dryness to yield the solid salt. Representative acids which may be used are formic, acetic, citric, picric, sulfuric, hydrochloric, hydrobromic, hydriodic, phosphoric, succinic, salicylic, and others. Acid addition salts may be formed with the nitrogen atom of the pyrrolidyl group in all of the compounds of the present invention, and quaternary ammonium acid addition products of the nitrogen atom of the hydrocarbazole radical, if such is present, may also be formed. Whether the mono- or di- addition salt is produced is dependent upon the relative proportions of the basic amine and salt-forming agent used in preparing the salt. Other compounds which may be used to form quaternary ammonium salts are alkyl halides, aralkyl halides, and alkyl esters of arylsulfonic acids, such as, for example, methyl iodide, methyl bromide, cetyl bromide, myristyl iodide, lauryl bromide, benzyl chloride, allyl bromide, ethyl (para-toluene)-sulfonic acid, et cetera, in which case the free amine and salt-forming agent are merely mixed together, heated to complete the reaction, and the salt thereafter isolated. The quaternary ammonium salts, are, in some instances, also valuable as surface-tension depressants and wetting agents.

The following examples are given to illustrate the present invention but are in no way to be construed as limiting.

Example 1.—9-[beta-(1-pyrrolidyl)-ethyl]-carbazole

A suspension of sodamide (prepared from 3.8 grams of sodium) and 25.1 grams of carbazole in 150 milliliters of dry xylene was heated, with stirring, for three hours at 130 degrees centigrade, whereafter 20.0 grams of beta-(1-pyrrolidyl)-ethyl chloride was added and the reaction heated under reflux, with stirring, for an additional eight hours. Upon cooling, the reaction mixture was filtered free of the sodium chloride formed during the condensation, the sodium chloride washed with about 200 milliliters of hot xylene, and the xylene washings added to the reaction mixture. The combined xylene solutions were extracted with dilute hydrochloric acid, the acid extract made basic with sodium hydroxide solution, and the light brown precipitate of crude 9-[beta-(1-pyrrolidyl)-ethyl]-carbazole collected. After air-drying, the product weighted 38.4 grams and melted at 80–81 degrees centigrade.

By dissolving the product in boiling commercial hexane in the presence of activated carbon, filtering, and cooling, there was obtained light-yellow needles of 9-[beta-(1-pyrrolidyl)-ethyl]-carbazole, melting at 80.5–81.0 degrees centigrade.

Analysis: Calculated for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.60. Found: 81.80, 7.47, 10.51.

Example 2.—9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole

When condensed and isolated according to the procedure of Example 1, there was obtained from 25.6 grams of 1,2,3,4-tetrahydrocarbazole, sodamide (obtained from 3.8 grams of sodium), and 20.0 grams of beta-(1-pyrrolidyl)-ethyl chloride, a product consisting of 37.0 grams of 9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole.

The monohydrochloride was prepared by passing dry hydrogen chloride into a solution of 9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole in anhydrous ether. The hydrochloride, when purified by crystallization from a mixture of ethyl acetate and ethanol and decolorizing with activated charcoal, was obtained as light-yellow needles melting at 232.5–233 degrees centigrade.

Analysis: Calculated for $C_{18}H_{25}Cl$: C, 70.91; H, 8.27; N, 9.19. Found: 70.74, 8.01, 9.42.

Example 3.—9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole

When condensed and isolated according to the procedure of Example 1, there was obtained from 7.5 grams of 1,2,3,4,10,11-hexahydrocarbazole, sodamide (obtained from 2.20 grams of sodium), and 7.37 grams of beta-(1-pyrrolidyl)-ethyl chloride, 7.2 grams of 9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole, distilling at 147–149 degrees centigrade under a pressure of 0.45 millimeter of mercury.

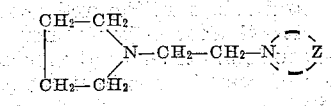
The monohydrochloride, obtained by passing dry hydrogen chloride into an ether solution of the free base, melted, after decolorization and crystallization from ethyl acetate, at 135–137.5 degrees centigrade.

Analysis: Calculated for $C_{18}H_{27}Cl$: C, 70.45; H, 8.87; N, 9.13; Cl, 11.55. Found: 70.40, 8.67, 9.07, 11.55.

Various modifications may be made in the present invention without departing from the spirit or scope thereof, and it is to be understood that I limit myself only as defined in the appended claims.

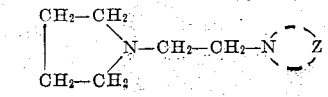
I claim:

1. A compound selected from the group consisting of (1) diamines of the formula:



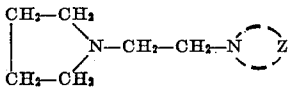
wherein Z is the remainder of a radical selected from the group consisting of (*a*) carbazole, and (*b*) hydrocarbazole radicals having up to and including four double bonds of the carbazole radical saturated with hydrogen, and (2) acid addition and quaternary ammonium salts thereof.

2. An acid addition salt of a diamine of the formula:



wherein Z is the remainder of a radical selected from the group consisting of (*a*) carbazole, and (*b*) hydrocarbazole radicals having up to and including four double bonds of the carbazole radical saturated with hydrogen.

3. A diamine of the formula:



wherein Z is the remainder of a radical selected from the group consisting of (*a*) carbazole, and (*b*) hydrocarbazole radicals having up to and including four double bonds of the carbazole radical saturated with hydrogen.

4. 9-[beta-(1-pyrrolidyl)-ethyl]-carbazole.

5. 9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole.

6. 9-[beta-(1-pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole monohydrochloride.

JOHN B. WRIGHT.

No references cited.