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N-PYRIDYL-4-AMINOALKOXY ANILINES

Jackson Pollard English, Princeton, and Frederick Louis Bach, Jr., Montvale, N.J., and Samuel Gordon, Pearl River, N.Y., assignors to American Cyanamid Company, Stamford, Conn., a corporation of Maine

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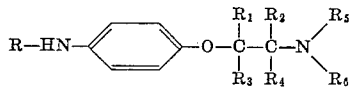
10 Claims. (Cl. 260—268)

This application is a division of our copending application Ser. No. 382,383, filed July 13, 1964, which in turn is a continuation-in-part of our application Ser. No. 310,466, filed Sept. 20, 1963, now abandoned, which in turn is a continuation-in-part of our application Ser. No. 218,135, filed Aug. 20, 1962, now abandoned.

This invention relates to certain novel disubstituted-amino-ethoxyphenyl amines and, more particularly, is concerned with novel compounds which may be represented by the following general formula:



wherein R_1, R_2, R_3 and R_4 are each hydrogen, methyl or ethyl with the proviso that the total number of carbon atoms in the alkylene group is less than 7; R_5 is lower alkyl; R_6 is lower alkyl; R_5 and R_6 taken together with the N(itrogen) is pyrrolidino, piperidino or 4-lower alkyl-1-piperazino; and R is 4-pyridyl, 3-nitro-2-pyridyl or 5-nitro-2-pyridyl. Lower alkyl groups contemplated by the present invention are those having from 1 to 4 carbon atoms. The invention includes the novel disubstituted-amino-ethoxyphenyl amines and the method of lowering therewith the cholesterol level in blood serum.

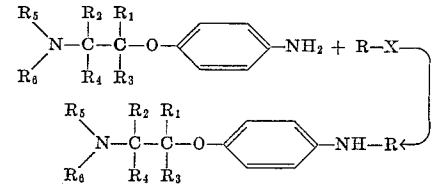
Atherosclerosis is a form of arteriosclerosis where cholesterol and lipoid materials are deposited as plaques in the intima of large and medium sized arteries. Arteriosclerosis is associated with the degeneration of arterial walls by mechanisms not clearly defined. However, there is a statistical correlaton between hypercholesteremia and the incidence of cardiovascular disease. For some time it has been considered desirable to lower high cholesterol and lipid levels as a possible preventive measure against atherosclerosis. In the past, attempts have been made to lower the level of cholesterol in the blood by the oral feeding of various substances which have been generally referred to in the art as hypocholesteremic adjuvants. Typical of such substances are lecithin, cottonseed oil and corn oil.

Our invention is based upon the discovery that our novel disubstituted-aminoethoxyphenyl amines exert a more powerful hypocholesteremic action than the adjuvants which have been used heretofore. It is not known how the novel compounds of the present invention operate to lower the cholesterol level in blood serum and no theory of why these compounds so operate is advanced. It is not intended that the present invention should be limited to any theory as to mechanism.

The method of administering the novel compounds of the present invention is limited to oral administration. They may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft gelatin capsules, or they may be compressed into tablets. It is an advantage of the present invention that our novel compounds may be orally administered in any convenient manner. The amount of a single dose or of a daily dose to be given will vary with the size of the individual to be treated, but should be such as to give a proportionate dosage of from 3 milligrams to 30 milligrams per kilogram of body weight

per day. In terms of total weight, this is usually from about 0.2 gram to about 2.0 grams per daily dosage unit.

The novel compounds of the present invention may be readily prepared by the interaction of a p-disubstituted-aminoethoxy aniline with a 4-halopyridine, a 2-halo-3-nitropyridine or a 2-halo-5-nitropyridine as set forth in the following reaction scheme:



wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are as previously defined and X is halogen. The reaction is preferably carried out in a solvent such as a lower alkanol, dioxane, tetrahydrofuran, and the like, at temperatures ranging from about 20° C. to about 100° C. over a period of time ranging from about 1 hour to 15 hours or more.

The organic bases of this invention form non-toxic acid-addition and quaternary ammonium salts with a variety of organic and inorganic salt-forming reagents. Thus, acid-addition salts, formed by admixture of the organic free base with an acid, suitably in a neutral solvent, are formed with such acids as sulfuric, phosphoric, hydrochloric, hydrobromic, sulfamic, citric, lactic, malic, succinic, tartaric acetic, benzoic, gluconic, ascorbic, and related acids. Quaternary ammonium salts may be formed by reaction of the free bases with a variety of organic esters of sulfuric, hydrohalic and aromatic sulfonic acids. The organic reagents employed for quaternary ammonium salt formation are preferably lower alkyl halides. However, other organic reagents are suitable for salt formation, and may be selected from among a diverse class of compounds including benzyl chloride, phenethyl chloride, naphthylmethyl chloride, dimethyl sulfate, methyl benzenesulfonate, ethyl toluenesulfonate, allyl chloride, methallyl bromide and crotyl bromide. For purposes of this invention the free bases are equivalent to their non-toxic acid-addition and quaternary ammonium salts.

The novel compounds of the present invention are, in general, colored materials which may be purified by distillation under reduced pressure. They are generally insoluble in water, but relatively soluble in organic solvents such as lower alkanols, esters, ethers, ketones, benzene, toluene, chloroform, and the like. The acid-addition and quaternary ammonium salts of the organic bases of the present invention are, in general, crystalline solids, relatively soluble in water, methanol and ethanol, but relatively insoluble in nonpolar organic solvents such as ether, benzene, toluene and the like.

The invention will be described in greater detail in conjunction with the following specific examples.

Example 1.—N-(4-pyridyl)-p-(2-diethylaminoethoxy) aniline

A solution of 9.6 g. of 4-bromopyridine hydrobromide and an excess of p-(2-diethylaminoethoxy)aniline in 100 ml. of ethanol was warmed for a short time and then concentrated to a semi-solid residue. This crude material was triturated with two 100-ml. portions of water, dissolved in ether and precipitated by the addition of petroleum ether. There was thus obtained the N-(4-pyridyl)-p-(2-diethylaminoethoxy)aniline as grey-green platelets, M.P. 125–127° C.

Example 2.—N-(3-nitro-2-pyridyl)-p-(2-diethylaminoethoxy)aniline

An ethanolic solution of 6.3 g. of 2-chloro-3-nitropyridine and 8.3 g. of p-(2-diethylaminoethoxy)aniline was

heated on a steam bath for one hour. After removing the solvent and treating the semi-solid residue with an excess of aqueous sodium hydroxide, recrystallization from ether-petroleum ether gave N-(3-nitro-2-pyridyl)-p-(2-diethylaminoethoxy)aniline, M.P. 47–48° C.

Example 3.—N-(5-nitro-2-pyridyl)-p-(2-diethylaminoethoxy)aniline

2-chloro-5-nitropyridine (7.9 g.) is added to 10.4 g. of p-(2-diethylaminoethoxy)aniline in 75 ml. of ethanol to form a deep-red solution. After standing 3 hours the ethanol is removed and the semi-solid red residue is treated with an excess of dilute ammonium hydroxide. The yellow granular precipitate is recrystallized from benzene-petroleum ether (30–60° C.) to yield the desired N-(5-nitro-2-pyridyl)-p-(2 - diethylaminoethoxy)aniline; M.P. 143–145° C. (sintering at 136° C.).

Example 4.—N-(5-nitro-2-pyridyl)-p-[(2-diethylamino-1-methyl)ethoxy]aniline

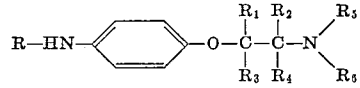
Sodium hydride (7.2 g.) is added to 131 g. of 1-diethylamino-2-propanol cooled to 0–10° C. After hydrogen evolution ceases 72.3 g. of 1-fluoro-4-nitrobenzene is added portionwise with stirring. The cold reaction mixture is then allowed to warm to room temperature with stirring, filtered and concentrated to a heavy, brown oil. The organic material is taken up in ether, treated with anhydrous hydrogen chloride gas and the granular monohydrochloride collected on a sintered glass filter. The hydrochloride is then dissolved in a minimum amount of water (approximately 100 ml.), decolorized with charcoal and neutralized with dilute sodium hydroxide solution. The basic, organic material is extracted with ether and the ether extract subjected to a fractional distillation. p-[(2-diethylamino-1-methyl)ethoxy]nitrobenzene is obtained as a yellow oil boiling at 130–135° C. (0.3–0.4 mm.). The product obtained in this manner is used in the next step without further purification.

Twelve grams of p-[(2-diethylamino-1-methyl)ethoxy]-nitrobenzene is dissolved in ethanol and reduced at room temperature and 35 p.s.i. of hydrogen using 5% palladium-on-charcoal catalyst. The desired p-[(2-diethylamino-1-methyl)-ethoxy]aniline is obtained as a yellowish oil boiling at approximately 147–149° C. (1.0 mm.). The aniline derivative obtained in this manner is used in the next step without further purification.

2-chloro-5-nitropyridine (3.8 g.) is added to 5.6 g. of p-[(2-diethylamino-1-methyl)ethoxy]aniline in 75 ml. of ethanol and the clear red solution is warmed at 70° C. for two hours; cooled to room temperature and allowed to stand 48 hours. Removal of the volatile materials leaves a red-brown oil which is dissolved in benzene (25 ml.) and placed on a 2.5-cm. x 50-cm. column packed with Florasil. After eluting the column with five 100-ml. portions of benzene-petroleum ether (30–60° C.) 40:60 the desired N-(5-nitro-2-pyridyl)-p-[(2-diethylamino - 1 - methyl) ethoxy]aniline is eluted from the column with ethyl acetate, and recrystallized from ether-petroleum ether (30–60° C.); M.P. 59–61° C.

What is claimed is:

1. A member of the class consisting of compounds of the formula:



wherein R is selected from the group consisting of 4-pyridyl, 3-nitro-2-pyridyl and 5-nitro-2-pyridyl; R_1, R_2, R_3 and R_4 are each selected from the group consisting of hydrogen, methyl and ethyl with the proviso that the sum of the carbon atoms of $R_1+R_2+R_3+R_4$ is less than 5; R_5 is lower alkyl; R_6 is lower alkyl; and R_5 and R_6 taken together with the N(itrogen) is selected from the group consisting of pyrrolidino, piperidino and 4-lower alkyl-1-piperazino; and the non-toxic acid-addition and quaternary ammonium salts thereof.

2. A compound according to claim 1 wherein R is 4-pyridyl; R_1, R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 are each ethyl.

3. A compound according to claim 1 wherein R is 3-nitro-2-pyridyl; R_1, R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 are each ethyl.

4. A compound according to claim 1 wherein R is 5-nitro-2-pyridyl; R_1, R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 are each ethyl.

5. A compound according to claim 1 wherein R is 5-nitro-2-pyridyl; R_1 is methyl; R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 are each ethyl.

6. A compound according to claim 1 wherein R is 4-pyridyl; R_1 and R_3 are each hydrogen; and R_2, R_4, R_5 and R_6 are each methyl.

7. A compound according to claim 1 wherein R is 4-pyridyl; R_1 is methyl; R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 are each ethyl.

8. A compound according to claim 1 wherein R is 3-nitro-2-pyridyl; R_1, R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 taken together with the N(itrogen) is pyrrolidino.

9. A compound according to claim 1 wherein R is 3-nitro-2-pyridyl; R_1, R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 taken together with the N(itrogen) is piperidino.

10. A compound according to claim 1 wherein R is 5-nitro-2-pyridyl; R_1, R_2, R_3 and R_4 are each hydrogen; and R_5 and R_6 taken together with the N(itrogen) is 4-methyl-1-piperazino.

References Cited

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ALEX MAZEL, *Primary Examiner.*

H. JILES, *Assistant Examiner.*