AMINOETHOXYPHENYL AMINE, ETHER, AND SULFIDE DERIVATIVES OF PYRINDINE

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

wherein R₁, R₂, R₃ and R₄ are each hydrogen, methyl or ethyl with the proviso that the total number of carbon atoms in the alkylene group is less than 7; R₅ is lower alkyl; R₆ is lower alkyl; and R₇ and R₈ taken together with the N at nitrogen is pyrroliodin, piperidin, morpholin, thiomorpholin or 4-lower alkyl-1-piperazino; Z is imino, oxygen or sulphur; and R is 4-pyridyl, 3-nitro-2-pyridyl, 5-nitro-2-pyridyl, 3-halo-2-pyridyl, 2-benzenethiozoyl, 2-halo-4-pyrimidin, 2,6-dihalo-4-pyrimidyl or a p-nitrophenyl group of the following general formula:

wherein R₇ is hydrogen, nitro or amino. Lower alkyl groups contemplated by the present invention are those having from 1 to 4 carbon atoms. Halogen is exemplified by chlorine and bromine. The invention includes the novel disubstituted aminooethoxyphenyl amines, ethers and sulfides 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 correlation between hypercholesteremia and the incidence of cardiovascular disease. For some time it has been considered desirable to lower high cholesterol and lipid levels in man 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 agents. Typical of such substances are lecithin, cottonseed oil, and corn oil.

Our invention is based upon the discovery that our novel disubstituted-aminooethoxyphenyl amines, ethers and sulfides exert a more powerful hypocholesteremic action than the adjuvants which have been used hitherto. 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 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.
2-halo-3-nitropyridine, or a 2-halo-5-nitropyridine is substituted for the p-nitrohalobenzene. The intermediate o- or p-hydroxynitrodiaryl ether is then treated with an appropriate disubstituted-aminooethyl halide whereby the desired disubstituted-aminooethyl halide is obtained. Advantageously, the intermediate o- or p-hydroxynitrodiaryl ether is first converted to its alkali metal alkoxide in an inert solvent such as toluene before treatment with the disubstituted-aminooethyl halide.

Certain of the novel disubstituted-aminooethyl halide sulphones of the present invention may be readily prepared by the interaction of phenol with an appropriate substituted p-nitrosulphenyl halide as set forth in the following reaction scheme:

\[
\text{R}_1\text{R}_2\text{HO} \quad + \quad \text{X-S-D-NO}_2\text{R} \quad \quad \text{HO} \quad + \quad \text{X-S-D-NO}_2\text{R} \quad \quad \text{R}_1\text{R}_2\text{HO-S-D-NO}_2\text{R}
\]

wherein \(\text{R}_1\) and \(\text{X}\) are as previously defined. The intermediate 4-hydroxy-4-nitrophenyl sulphide so obtained is then treated with an appropriate disubstituted-aminooethyl halide whereby the desired disubstituted-aminooethyl halide sulphide is obtained. Again, it is preferred to convert the intermediate 4-hydroxy-4-nitrophenyl sulphide to its alkali metal alkoxide in an inert solvent such as toluene prior to reaction with the disubstituted-aminooethyl halide.

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, hydrofluoric, nitric, 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, hydrochloric, 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, phenetyl chloride, naphthylmethyl chloride, dimethyl sulfate, methyl benzzenesulfonate, 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 non-polar 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**

4'-2-diethylaminoethoxy)-4-nitrodiphenylamine

A solution of 4.2 g. of 2-diethylaminoethoxy)-aniline and 3.6 g. of potassium 2-chloro-5-nitrobenzoate in 50 mL of water and 50 mL of ethanol was refluxed for 15 hours and then extracted with two 100-mL portions of chloroform. The aqueous raffinate was acidified with dilute hydrochloric acid whereupon a precipitate formed which was removed by filtration and dried. There was thus obtained 2.1 g. of crude 4'-2-diethylaminoethoxy)-4-nitrodiphenylamine which was placed in a distillation flask packed with glass beads and heated under reduced pressure. The solid mass melted and began effervescing at 180°C (0.1 mm.). When decarboxylation was complete, the reaction mixture was cooled and triturated with sodium hydroxide solution. This crude solid was recrystallized from ethanol whereby there was obtained 4'-2-diethylaminoethoxy)-4-nitrodiphenylamine, M.P. 86-88°C.

**EXAMPLE 2**

4'-2-diethylaminoethoxy)-2,4-dinitrodiphenylamine

A solution of 4.2 g. of p-2-diethylaminoethoxy)-aniline and 2.8 g. of 2,4-dinitrofluorobenzene in 100 mL of ethanol was refluxed for 3 hours. The reaction mixture was then poured onto crushed ice, the insoluble red solid which separated was collected by filtration, and this crude material was recrystallized from ethanol whereby there was obtained 4'-2-diethylaminoethoxy)-2,4-dinitrodiphenylamine, M.P. 70-71°C.

**EXAMPLE 3**

2'-2-diethylaminoethoxy)-2,4-dinitrodiphenylamine

A solution of 4.2 g. of o-2-diethylaminoethoxy)-aniline and 2.8 g. of 2,4-dinitrofluorobenzene in 100 mL of ethanol was refluxed for 4 hours. The reaction mixture was then worked up as described in Example 2 to yield 2'-2-diethylaminoethoxy)-2,4-dinitrodiphenylamine, M.P. 90-91°C.

**EXAMPLE 4**

4'-2-diethylaminoethoxy)-2-amino-4-nitrodiphenylamine

Alcoholic ammonium sulfide was added to a refluxing ethanolic solution of 4'-2-diethylaminoethoxy)-2,4-dinitrodiphenylamine. The cooled reaction mixture was treated with charcoal and filtered, and the filtrate was dried over anhydrous sodium carbonate. Passing dry hydrogen chloride gas through the dried filtrate precipitated the desired 4'-2-diethylaminoethoxy)-2-amino-4-nitrodiphenylamine dihydrochloride, M.P. 179-181°C.

**EXAMPLE 5**

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 6**

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 7**

4'-2-diethylaminoethoxy)-4-nitrodiphenyl ether

A mixture of 3.3 g. of p-hydroquinone, 1.2 g. of sodium hydroxide and 4.2 g. of 4-nitrofluorobenzene was refluxed for 15 hours and then cooled to room temperature. On standing, the desired intermediate, 4'-2-diethylaminoethoxy)-4-nitrodiphenyl ether, precipitated as a yellow granular solid. This intermediate was treated with 0.7 g. of sodium hy-
dride in toluene followed by 4.1 g. of diethylaminoethyl chloride in toluene. Concentration of the reaction mixture gave a yellow oil which was purified by vacuum distillation. There was thus obtained the 4'-(-2-diethylaminoethoxy) -4-nitrodiphenyl ether, B.P. 170-175° C./0.2 mm.

EXAMPLE 8

4'-(2-diethylaminoethoxy)-4-nitrodiphenyl sulfide

A solution of 11.2 g. of 4-nitrophenylsulfonyl chloride and 56 g. of phenol in 100 ml. of dry ether was allowed to stand overnight at room temperature. Concentration of the solution gave the desired intermediate, 4'-hydroxy-4-nitrodiphenyl sulfide, as a yellow solid. A toluene solution of this intermediate was treated with sodium hydride and then refluxed for 3 hours. The red brown suspension thus obtained was refluxed an additional 3 hours with diethylaminoethyl chloride whereby the desired 4'-(2-diethylaminoethoxy)-4-nitrodiphenyl sulfide was obtained as a yellow oil.

EXAMPLE 9

N-(2,6-dichloro-4-pyrimidyl)-p-(2-diethylaminoethoxy) aniline

2,4,6-trichloropyrimidine (5.1 g.) and 6.2 g. of p-(2-diethylaminoethoxy)aniline are added to 15 g. of phenol and warmed at 75-80° C. for 3 hours. The phenolic solution is then poured on crushed ice and worked up as described above. The desired N-(2,6-dichloro-4-pyrimidyl)-p-(2-diethylaminoethoxy)aniline is obtained by two recrystallizations from a benzene solution; M.P. 104-106° C.

EXAMPLE 10

N-(2-chloro-4-pyrimidyl)-p-(2-diethylaminoethoxy) aniline

A solution consisting of 6.2 g. of p-(2-diethylaminoethoxy)aniline and 4.4 g. of 2,4-dichloropyrimidine in 75 ml. of ethanol is warmed to 70° C. and then allowed to stand overnight. After distilling off the volatile materials the remaining dark-brown oil is warmed with 250 ml. of water and the aqueous layer is separated; extracted with two 50 ml. portions of ether, and then neutralized with dilute ammonium hydroxide. The desired N-(2-chloro-4-pyrimidyl)-p-(2-diethylaminoethoxy)aniline is obtained as a gray-white solid melting at 75-77° C.

EXAMPLE 11

N-(3-chloro-2-pyrimidyl)-p-(2-diethylaminoethoxy) aniline

A solution consisting of 3.7 g. of 2,5-dichloropyrimidine and 5.2 g. of p-(2-diethylaminoethoxy)aniline in 25 ml. of ethanol is heated at 70° C. for three hours; cooled to room temperature and then worked up as described in Example 10. The desired aniline, N-(3-chloro-2-pyrimidyl)-p-(2-diethylaminoethoxy)aniline is recrystallized from ether-petroleum ether (30-60° C.); M.P. 92-94° C.

EXAMPLE 12

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 and form to 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 13

2-[p-(2-diethylaminoethoxy)anilino] benzothiazole

A solution consisting of 17.0 g. of 2-chlorobenzonitrobenzole and 20.8 g. of p-(2-diethylaminoethoxy)aniline in 200 ml. of ethanol is refluxed for 15 hours, and then concentrated to a semi-solid residue. The residue is made basic with 10% potassium hydroxide solution, and with two 100 ml. portions of ether, and the ether extract is combined, decolorized with charcoal and dried over anhydrous sodium sulfate. After removing the low boiling materials the residual oil is distilled in vacuo until no more p-(2-diethylaminoethoxy)aniline is present over. The pot-residue is recrystallized from an ether-petroleum ether (30-60° C.) solution to give 2-[p-(2-diethylaminoethoxy)anilino]benzothiazole; M.P. 92-94° C.

EXAMPLE 14

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 27.3 g. of 1-chloro-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 mono-hydrochloride collected on a sintered glass. 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 (in vac.). 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; 35 p.s.i. of hydrogen using 5% palladium-on-charcoal catalyst. The desired p-(2-diethylamino-1-methyl)ethoxy)nitrobenzene 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 distillation.

N-(5-chloro-2-pyrimidyl)-p-(2-diethylaminoethoxy)aniline is added to 5.6 g. of 2-chloro-5-nitropyridine (3.8 g.) and placed on a 2.5-cm. x 50-cm. column packed with Florisil. 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.

EXAMPLE 15

N-(5-chloro-2-pyrimidyl)-p-(2-dimethylamino-2,2- dimethyl)ethoxy)aniline

A Pyrex tube was charged with 6.3 g. of p-(2-dimethylamino-2,2-dimethyl)ethoxy)aniline and 3.9 g. of 2,5-dichloropyrimidine, flushed with dry argon and sealed. After heating the mixture for 15 hours the semi-solid residue was dissolved in water, decolorized with charcoal, and made basic with dilute sodium hydroxide solution. The insoluble material was collected, dissolved in benzene and chromatographed on Florisil which was eluted with benzene-petroleum ether (30-60° C.) 8:2. The benzene-petroleum ether eluates were combined and concentrated to a residue which was recrystallized from a benzene-petroleum ether (30-60° C.) solution to give the desired product N-(5-chloro-2-pyrimidyl)-p-(2-dimethylamino-2,2-dimethyl)ethoxy)aniline; M.P. 120-121° C.
EXAMPLE 16

N-(5-chloro-2-pyrimidyl)-p-(2-pyrrolidinoethoxy)aniline

Using the procedure described in Example 15, 8.3 g. of p-(2-pyrrolidinoethoxy)aniline and 6.0 g. of 2,5-dichloropyrimidine were heated in a sealed tube under argon for 15 hours. The desired product N-(5-chloro-2-pyrimidyl)-p-(2-pyrrolidinoethoxy)aniline was isolated by passing a benzene solution of the crude reaction mixture through a Florisil column.

What is claimed is:
1. N - (2,6-dichloro-4-pyrimidyl)-p-(2-diethylaminoethoxy)aniline.
2. N - (2-chloro-4-pyrimidyl) - p-(2-diethylaminoethoxy)aniline.
3. N - (5-chloro-2-pyrimidyl) - p-(2-diethylaminoethoxy)aniline.
6. A member of the class consisting of compounds of the formula:

\[
\begin{array}{c}
\text{R} - \text{Z} - \text{N} - \text{R}_1 \\
\text{R}_2 - \text{C} - \text{R}_3 \\
\text{R}_4 - \text{R}_5
\end{array}
\]

wherein \( \text{R}_1, \text{R}_2, \text{R}_3 \) and \( \text{R}_4 \) are each selected from the group consisting of hydrogen, methyl and ethyl with the proviso that the sum of the carbon atoms of \( \text{R}_1 + \text{R}_2 + \text{R}_3 + \text{R}_4 \) is less than 5; \( \text{R}_3 \) is lower alkyl; \( \text{R}_4 \) is lower alkyl; \( \text{R}_5 \) and \( \text{R}_6 \) taken together with the N-heteroatom is selected from the group consisting of pyrrolidino, piperidino, morpholino, thiomorpholino and 4-lower alkyl-1-piperazino; \( Z \) is selected from the group consisting of imino, oxygen and sulfur; and \( R \) is selected from the group consisting of 5-halo-2-pyrimidyl, 2-halo-4-pyrimidyl and 2,6-dihalo-4-pyrimidyl; and the non-toxic acid-addition and quaternary ammonium salts thereof.


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