HETEROCYCLIC AMINO PHENOXYACETIC ACIDS, ACID ADDITION SALTS AND QUATERNARY AMMONIUM SALTS THEREOF


No Drawing. Filed Feb. 18, 1963, Ser. No. 259,460

3 Claims. (CL. 260—294)

This application is a continuation in part of application S.N. 818,548 filed June 8, 1959, now abandoned.

This invention relates to heterocyclic amino substituted phenoxyacetic acid compounds in which the heterocyclic amino group is attached to the phenyl ring through a ring nitrogen atom, and includes correlated improvements and discoveries whereby novel compounds having useful characteristics are provided.

A principal object of this invention is to provide novel heterocyclic amino substituted phenoxyacetic acid compounds, including the acids, esters, amidines, salts, acid addition salts and quaternary ammonium salts.

Another object of the invention is to provide compositions which are particularly effective for reducing the cholesterol level of blood, containing heterocyclic amino substituted phenoxyacetic acid compounds, esters, amidines and related compounds.

In accordance with this invention, it has been determined that phenoxyacetic acid compounds having a heterocyclic amino group attached to the phenyl nucleus through a ring nitrogen atom are particularly effective as hypcholesteremic agents. The heterocyclic amino group preferably contains at least about four carbon atoms and may also contain other heterocyclic substituents, such as nitrogen, oxygen and sulfur, either as part of the ring or attached to other atoms which are part of the ring. Preferably the heterocyclic amino group has from four to ten atoms in the ring, of which from one to three, preferably one, should be heterocyclic atoms, the remainder being carbon atoms. The heterocyclic amino group can be substituted in any position on the phenyl nucleus, ortho, meta or para to the oxyacetic acid group.

The alpha carbon atom of the acetic acid group attached through an oxygen atom to the phenyl nucleus can be substituted or unsubstituted. If substituted, it is preferably substituted with a lower alkyl group having from 1 to 6 carbon atoms.

Suitable heterocyclic amino phenoxyacetic acid compounds of this invention are the phenoxyacetic acids and the esters and amidines of the phenoxyacetic acids with lower alkyl alcohols, cycloalkyl alcohols, lower alkanolamines, ammonia and lower alkyl amines.

The phenoxyacetic acid compounds of this invention can be defined by the following formula:

\[
\text{R}_1 \text{O} - \text{CH} = \text{O} - \text{R}_2
\]

In the above formula, \( \text{R}_1 \) can be hydrogen or a lower alkyl group having from 1 to 6 carbon atoms, \( \text{R}_2 \) can be selected from the group consisting of hydroxy, lower alkoxyl, cycloalkoxy preferably having from 5 to 7 carbon atoms, hydrazino, methyl hydrazyl, ethyl hydrazyl, propyl hydrazyl, mono- and di-lower alkyl-hydrazino, amino of the formula

\[
\text{NH}_2
\]

and lower oxyalkyl amino of the formula

\[
\text{N} - \text{O} - (\text{lower alkyl})_n
\]

wherein \( \text{R}_3 \) and \( \text{R}_4 \) can each be hydrogen, lower alkyl, mono- and di-(lower alkyl)-amino-lower alkyl and amino-lower alkyl [e.g. \(-\text{C}_2\text{H}_5-\text{NH}_2\)].

In the above formula is a heterocyclic group having from 4 to 10 atoms, preferably 5 to 7 atoms, in the ring, from one to three ring atoms thereof, preferably from one to two, being selected from the group consisting of nitrogen, oxygen and sulfur, at least one being nitrogen, the remaining ring atoms being carbon. The ring atoms can be unsubstituted or substituted with inert groups such as lower alkyl, hydroxy and carbonyl or keto oxygen, \( =\text{O} \). The total number of carbon atoms in the group preferably does not exceed about 15.

It will be evident from the foregoing that the phenoxyacetic acid compounds of the invention are acids when \( \text{R}_2 \) is \( \text{OH} \), esters when \( \text{R}_3 \) is alkoxy or cycloalkoxy or oxyalkylene, and amidines when \( \text{R}_3 \) is amine. The term "acid compound" is used generically herein to refer to all of these subgenera of the invention.

Thus, in the foregoing formula, \( \text{R}_1 \), \( \text{R}_3 \) and \( \text{R}_4 \) can each be, for example, hydrogen, methyl, ethyl, \( n \)-propyl, isopropyl, \( n \)-butyl, iso-butyl, t-butyl and any of the pentyl and hexyl isomers. \( \text{R}_3 \) can, for example, be hydroxy, methoxy, ethoxy, \( n \)-proproxy, iso-proproxy, \( n \)-butoxy, iso-butoxy, \( t \)-butoxy and any of the isomeric pentoxy and hexoxy derivatives, cyclopentoxy, cyclohexoxy and cycloheptoxy, amido, monoethylenamido, dimethylamino, monoethylamino, diethylenimino, monoiso-propylaminio, di-isopropylamino, mono- \( n \)-propylamino, di- \( n \)-propylamino, mono- \( n \)-butylamino, di- \( n \)-butylamino, mono-t-butylamino, di-t-butylamino, monopentylamino, dipentylamino, monohexylamino, dihexylamino, \( =\text{O} - \text{CH}_2 - \text{CH}_2 - =\text{NH}_2 \), \( =\text{O} - (\text{CH}_2)_2 =\text{NH}_2 \), \( =\text{O} - \text{CH}_3 - \text{CH}_2 - =\text{NH}_2 \), etc.

Some of the above substituents have been described as the amino of the form

\[
\text{NH}_2
\]

and lower oxyalkyl amino of the form

\[
\text{N} - \text{O} - (\text{lower alkyl})_n
\]

wherein \( \text{R}_3 \) and \( \text{R}_4 \) can each be hydrogen, lower alkyl, mono- and di-(lower alkyl)-amino-lower alkyl and amino-lower alkyl [e.g. \(-\text{C}_2\text{H}_5-\text{NH}_2\)].
and

Thus

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

in which the Q groups are alkylene groups containing from one to about ten carbon atoms, \(n\) is zero or one and the total number of ring atoms in the group ranges from about four to about ten. Representative groups include

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

\[
\begin{align*}
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,} \\
N - \bigg\{ & \text{Q,}
\end{align*}
\]

The following compounds are illustrative of compounds coming within the scope of the invention:

(1)

(2)

(3)

(4)

(5)

(6)

(7)

(8)
The compounds of this invention can be prepared by any of several procedures. The appropriate dihaloalkane can be condensed with an aminophenol to yield the required heteroamino phenol which can then be condensed with ethyl-alpha-halo acetates to give the substituted phenoxycetates which can then be converted to any desired esters or amides, in accordance with conventional procedures. Equations for the foregoing preparations are as follows, with X being halogen:

(I) (a) OH
              NH₄⁺ + X⁻ + O
(b) OH

The acetate ester thus obtained can be hydrolyzed to form the acid, can be transesterified with an alcohol of the formula R₂OH to form the appropriate ester, can be reacted to form amides with ammonia and with primary or secondary amines, and with hydrazines. In an alternative procedure, the compounds of this invention can be prepared by condensing a nitrophenol with an ethyl-alpha-halo alkanoate, reducing the resultant nitrophenoxycetate to the aminophenoxycetate and cyclizing the amino group to form a heterocyclic group. Reduction and ring closure can take place either prior to or after esterification or amide formation. An equation for this preparation is as follows:

(II) (a) OH
               NO₃⁺ + X⁻ + O
(b) OH

The resultant compounds can be reacted with any pharmaceutically acceptable inorganic or organic acid to form non-toxic pharmaceutically acceptable acid addition salts such as hydrochlorides, hydrobromides, nitrates, sulfates, phosphates, acetates, formates, tartrates, malates, threophyllinates, 8-chlorotheophyllinates, and the like. Similarly, through the use of selected quaternizing agents, such as alkyl sulfates and alkyl halides, e.g., methyl iodide, ethyl bromide, methyl p-toluene-sulfonate, alkyl bromide, ethyl bromoacetate, and the like, non-toxic pharmaceutically acceptable quaternary salts of the novel compounds are readily prepared.

These quaternary salts can be represented by the formula:

wherein R₄ is selected from the group consisting of hydrogen and an organic radical having from one to eight carbon atoms such as methyl, ethyl, propyl, butyl, ocyl, allyl, pentyl, benzyl and carboethoxyalkyl such as carbethoxymethyl, and A is an inert non-toxic pharmaceutically acceptable anion, such as bromide, iodide, chloride and p-toluenesulfonate.

When R₄ contains a nitrogen atom, the quaternary salt can be formed at that nitrogen atom or at both the R₄ nitrogen atom and the heterocyclic nitrogen atom. The quaternary ammonium salts can be prepared by conventional methods as by refluxing equivalent quantities of the appropriate amino substituted phenoxycetic acid with an alkyl halide or an alkyl sulfate in an inert solvent such as ethanol or benzene. The quaternary ammonium salts generally crystallize out on standing. Where crystallization does not occur, the solution can be cooled or an additional hydrocarbon solvent such as hexane can be added in accordance with conventional techniques. Where the double quaternary salt is desired, two equivalents of the alkyl halide or alkyl sulfate can be added.

The acid addition salts are prepared by reacting equivalent quantities of the amino substituted phenoxycetic acid and the desired acid in an inert solvent such as ethanol or benzene and recovering the acid addition salt by conventional means.

The following working examples illustrate the best modes of preparing the compounds of this invention.

**EXAMPLE I**

A mixture of 102 g. (0.84 mole) of o-anisidine, 180 g. (0.84 mole) of 1,4-dibromobutane, 172 g. (1.12 mole) of sodium carbonate and 900 mL. of acetone were refluxed with stirring for 34 hours. After filtering off the salts, the solution was evaporated down and the residue taken up in dilute hydrochloric acid. The solution was
washed with ether, then made basic with dilute sodium hydroxide and the resulting oil extracted into three portions of ether. These were combined, dried over anhydrous magnesium sulfate, then filtered, the solvent evaporated off and the residue distilled to give 103 g. of o-(1-pyrrolidinyl)anisole, boiling at 127–130° at 5 mm. 10 g. of the o-(1-pyrrolidinyl)anisole so prepared and 50 ml. of constant boiling hydrochloric acid were refluxed together for 28 hours, then treated with sodium iodide to distill out as formed. At the end of this time, the hydrochloric acid was removed at diminished pressure leaving a clear, thick oil. This was dissolved in water, the solution made basic with a saturated, aqueous solution of sodium bicarbonate and the resulting precipitate filtered off to yield o-(1-pyrrolidinyl)phenol, melting at 109–111°. The compound was purified by fractional crystallization from ether, cleaning to give a low melting Filtra-.

3,218,328.

EXAMPLE II

3-dimethylaminopropylamine (7.5 g., 0.075 mole), 3 g. (0.015 mole) of ethyl-α-[o-(1-pyrrolidinyl)phenoxy] acetate and 10 drops of 25% methanolic sodium methyate were heated in an oil bath at 140° C. for a total of 17 hours. From time to time, the bath was raised to 160° C. to distill out the ethanol formed. After cooling, pentane was added to the reaction mixture and a small quantity of insoluble material filtered off. The pentane filtrate was then evaporated down with the excess 3-dimethylaminopropylamine being distilled off. The product remaining which boiled at 178–182° C. at 0.005 mm. (mp = 1,5474), was identified as α-[o-(1-pyrrolidinyl)phenoxy]-N-(3-dimethylaminopropyl) acetamide.

EXAMPLE III

A solution of 33.4 g. (0.2 m.) of ethyl bromoacetate in 50 mls. of acetone was slowly added to a stirred mixture of 27.4 g. (0.2 m.) of m-nitrophenol, 27.6 g. of anhydrous potassium carbonate and 150 g. of acetone. After refluxing and stirring for 7 hours, the solid was filtered off, the solvent evaporated off from the filtrate and the residue distilled to give 41.9 g. (93%) of ethyl-2-(m-nitrophenoxy) acetate. A solution of 41.9 g. (0.19 m.) of the ethyl 2-(m-nitrophenoxy)acetate in 208 mls. of ethanol with 0.5 g. of tin bromide. This solution was then added to a mixture of ethyl acetate and hexane at an internal pressure of 3 atmospheres. Hydrogen uptake was complete (105%) after 70 minutes of shaking. After removal from the hydrogenator and filtration, the solvent was removed at diminished pressure, the residue taken up in dry ether and treated with dry hydrochloric chloride. Filtration yielded 38 g. melting at 125–135°. Recrystallization from acetonitrile gave 33 g. of ethyl 2-(m-aminoxy)acetate hydrochloride. A mixture of 8.0 g. (0.034 m.) of the ethyl 2-(m-aminoxy)acetate hydrochloride and 5.4 g. (0.051 m.) of anhydrous sodium carbonate and 30 mls. of ace tone and 30 mls. of water added, while a solution of 7.4 g. (0.034 m.) of 1,4-dibromo butane in 20 mls. of acetone was slowly added. Stirring was continued while refluxing for 27 hours. Filtration, removal of solvent and distillation gave 5.9 g. (70%) of product, boiling at 150–154° at 0.2 mm. The distillate solidified slowly on cooling to give a low melting

solid identified as ethyl 2-(m-pyrrolidinyl)phenoxyacetate. Anal.—Calc. for C14H13NO: N, 5.6. Found: N, 5.4.

EXAMPLE IV

By following the procedure set forth in Example III, but using 1,5-dibromopentane in place of 1,4-dibromobutane, the corresponding piperidinyl derivative, ethyl 2-(m-piperidinylphenoxy) acetate, was obtained.

EXAMPLE V

Additional compounds were prepared in accordance with the procedure of Examples I and II. The melting points of representative compounds are listed in Table I:

<table>
<thead>
<tr>
<th>Compound No. (as listed above)</th>
<th>Recrystallization Solvent</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>133–134</td>
</tr>
<tr>
<td>7</td>
<td>Ethanol</td>
<td>78–81</td>
</tr>
<tr>
<td>12</td>
<td>Acetonitrile</td>
<td>134–137</td>
</tr>
<tr>
<td>22</td>
<td>Ethanol</td>
<td>60–65</td>
</tr>
<tr>
<td>26</td>
<td>Heptane</td>
<td>77–97</td>
</tr>
<tr>
<td>28</td>
<td>Hexane</td>
<td>97–98</td>
</tr>
<tr>
<td>32</td>
<td>Ethanol</td>
<td>98–99</td>
</tr>
<tr>
<td>37</td>
<td>Heptane</td>
<td>98–99</td>
</tr>
<tr>
<td>41</td>
<td>Ethanol</td>
<td>98–99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound No. (as listed above)</td>
</tr>
<tr>
<td>128–131</td>
</tr>
<tr>
<td>178–182</td>
</tr>
<tr>
<td>185–190</td>
</tr>
<tr>
<td>195–199</td>
</tr>
<tr>
<td>142–144</td>
</tr>
<tr>
<td>135–138</td>
</tr>
<tr>
<td>164–168</td>
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<tr>
<td>176–182</td>
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<tr>
<td>164–188</td>
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<tr>
<td>156–183</td>
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<tr>
<td>170–180</td>
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<tr>
<td>156–183</td>
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<tr>
<td>156–195</td>
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<tr>
<td>149–144</td>
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<tr>
<td>156–195</td>
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<tr>
<td>156–195</td>
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<tr>
<td>156–195</td>
</tr>
<tr>
<td>156–195</td>
</tr>
<tr>
<td>176–182</td>
</tr>
<tr>
<td>176–182</td>
</tr>
<tr>
<td>203–204</td>
</tr>
</tbody>
</table>

The compounds of this invention can be used to reduce the cholesterol level of blood either directly or preferably by incorporating into a hypcholesteremic composition.

In addition to the heterocyclic amino phenoxycetic acid compound, the hypcholesteremic compositions of the invention include a carrier which can be water, an organic solvent, or other diluent, a cream or emulsion base of conventional formulation or a solid carrier such as is used in the formulation of tablets and capsules. The compositions can be formulated so as to be administered orally or parenterally. By such methods these compositions have the ability to markedly reduce the cholesterol level of blood in animals. The toxicity of these compounds is quite low, and the active ingredient can be administered in
dosages adequate to obtain a therapeutic effect without adverse side effects. The concentration of the phenoxyacetic acid compound in these compositions is not in any way critical, but can be adjusted to meet the need. In general, the concentration for oral and parenteral administration will lie within about 1 to about 500 mg. per unit dosage, i.e., per cc. of solution or per tablet or capsule, depending upon the dosage regimen desired and the weight and hypercholesteremic state of the animal. Ordinarily, it is preferable to administer a composition having a low concentration of the active ingredient several times daily, as compared to a single daily dose having a relatively high concentration of the active ingredient, to achieve the total daily dosage required. The daily dosage is generally within the range of about 25 to about 300 mg. of acid compound.

In the process of the invention, the heterocyclic amino phenoxyacetic acid compound or mixture thereof in an appropriate amount to obtain a therapeutic effect is administered to the patient orally, parenterally or by any other appropriate method, and there results a hypercholesteremic response. The examples illustrate various types of compositions coming within the invention for a variety of administration techniques.

**EXAMPLE VII**

A composition of matter for oral administration, comprising ethyl 1-(1-pyrrolidinyl)phenoxyacetic acid as the active ingredient in combination with a suitable carrier, was prepared by thoroughly mixing together 1000 grams of the active compound and 3500 grams of lactose (milk sugar), passing the blended mixture through a No. 40 screen and filling the mix into gelatin capsules, 450 mg. per capsule, each capsule to contain 100 mg. of active ingredient.

**EXAMPLE VIII**

A composition of matter for oral administration, in tablet form, comprising cyclohexyl (m-1-pyrrolidinyl) phenoxy isopropionate as the active ingredient in combination with a suitable carrier, was prepared by compounding the following ingredients into a tablet mix:

<table>
<thead>
<tr>
<th>Grams</th>
<th>Active ingredient</th>
<th>Sugar</th>
<th>Lactose</th>
<th>Starch</th>
<th>Dextrin</th>
<th>Talcum</th>
<th>Stearic acid</th>
<th>Starch paste q.s. to make 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>308</td>
<td></td>
<td>308</td>
<td>177</td>
<td>98</td>
<td>50</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

The above mix was compressed into tablets, weighing approximately 325 mg., each tablet containing 100 mg. of active ingredient.

**EXAMPLE IX**

A composition of matter for parenteral administration comprising m-(1-pyrrolidinyl) phenoxy methylacetamide as the active ingredient in combination with a liquid carrier having the following formula was prepared:

<table>
<thead>
<tr>
<th>Grams</th>
<th>Active ingredient</th>
<th>Sodium hydroxide</th>
<th>Benzyl alcohol</th>
<th>Water, pyrogen-free, q.s. to 500 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td></td>
<td>5.74</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

In making this solution the active ingredient was dissolved in 400 ml. of pyrogen-free water containing the sodium hydroxide, the benzyl alcohol added, and the solution was made up q.s. to 500 ml.; after which the solution was filtered aseptically and filled aseptically in ampules containing 1 ml., under a nitrogen atmosphere. The resulting solution supplied a dosage unit of 50 mg. of active ingredient.

Compositions of matter similar to those described under Examples V, VI and VII may be made by including other substances having therapeutic properties which enhance the total therapeutic value of the heterocyclic amino phenoxyacetic acid compound by their additive or by a synergistic effect; the effect, if synergistic, will enhance the therapeutic value of the heterocyclic amino phenoxyacetic compound without increase in dosage. Thus, known therapeutic substances, such as aspirin or equivalent salicylate compound, may be added for their analgesic and anti-inflammatory effect, butazoldin or antipyrine or related compounds for their anti-pyretic and anti-phlogistic effects, hydrocortisone or predniisolone or one of its equivalent corticosteroids for their anti-inflammatory, antiphlogistic effects. The combination of a heterocyclic amino phenoxyacetic acid compound with one or more of the above additive substances also serves the purpose of an additive effect.

If desired, other substances, such as ascorbic acid, vitamin K, thiamine, etc., may be added to the composition of matter in adequate dosage to exert their individual activity for therapeutic uses they are known to have.

If desired, the hypercholesteremic compositions can be sterilized and can contain auxiliary substances such as buffering agents, stabilizing agents, wetting agents and emulsifying agents.

To illustrate the therapeutically useful of the compounds of this invention in reducing the cholesterol level of blood, normal adult guinea pigs were given subcutaneous doses corresponding to 30 mg./kg. of the test compound at the beginning of the experiment, 24 hours later and finally, 48 hours later.

Blood samples were drawn for the determination of serum cholesterol levels at the initiation of the experiment and at 48, and 72 hours thereafter.

The hypercholesteremic response is indicated in Table III. In this table, the compound is identified by its number in the list above. The LD<sub>50</sub> indicates the minimum dose which is lethal to mice when the compound is administered subcutaneously and is expressed in mg./kg. The dose is the dosage of the drug administered subcutaneously expressed mg./kg. under the schedule described above and the effect of the compound in reducing cholesterol is indicated by the percent reduction from the cholesterol level noted for the animal at the initiation of the experiment (percent hypercholesterolemia).

Thus, if at the initiation of the experiment the noted cholesterol level was 80 mg. percent and at a subsequent interval, the noted cholesterol level was 60 mg. percent, this would be shown as 25% hypercholesterolemia.

**Table III**

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt;, mg./kg.</th>
<th>Percent Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,000</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>1,000</td>
<td>49</td>
</tr>
<tr>
<td>11</td>
<td>1,000</td>
<td>29</td>
</tr>
<tr>
<td>16</td>
<td>500</td>
<td>17</td>
</tr>
<tr>
<td>19</td>
<td>750</td>
<td>41</td>
</tr>
<tr>
<td>22</td>
<td>350</td>
<td>39</td>
</tr>
<tr>
<td>24</td>
<td>1,000</td>
<td>17</td>
</tr>
<tr>
<td>27</td>
<td>1,000</td>
<td>41</td>
</tr>
<tr>
<td>30</td>
<td>500</td>
<td>12</td>
</tr>
<tr>
<td>33</td>
<td>1,000</td>
<td>22</td>
</tr>
</tbody>
</table>

It will be noted that certain of the compounds tested were fast acting while others showed a more sustained action or a delayed action. In many cases it is desirable to employ a mixture of several compounds to obtain both rapid and sustained overall hypercholesteremic response. It is evident from Table III that the compounds of this invention show substantial hypercholesteremic activity at dosage levels substantially below the minimum lethal doses. A considerable reduction of cholesterol levels is...
obtained at substantially 1/2 of the LD_{50} for many of the compounds.

Under clinical conditions the rapidity of the depression of cholesterol levels obtained in the tests reported above would not be required so that even smaller doses could be used, thereby increasing the margin of safety.

The compounds of this invention in addition to their hypocholesteremic activity are also useful intermediates in the production of other compounds and also have utility as muscle relaxants and anti-inflammatory agents.

We claim:

1. A compound selected from the group consisting of those having the formula

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{CHCOOH}
\end{array}
\]

wherein R_{1} is selected from the group consisting of hydrogen and lower alkyl, and

\[
\text{N} \quad \begin{array}{c}
\text{CHCOOH}
\end{array}
\]

is selected from the group consisting of X-pyrrolidino, X-piperidino, X-hexamethyleneimino, X-morpholino, X-thiomorpholino, and X-octamethyleneimino, wherein X is selected from the group consisting of hydrogen, lower alkyl, hydroxy and acetyl; and the non-toxic acid addition salts and quaternary ammonium salts thereof.

2. A compound in accordance with claim 1 wherein

\[
\text{N} \quad \begin{array}{c}
\text{CHCOOH}
\end{array}
\]

is pyrrolidino.

3. A compound in accordance with claim 1 wherein

\[
\text{N} \quad \begin{array}{c}
\text{CHCOOH}
\end{array}
\]

is piperidino.

References Cited by the Examiner

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<table>
<thead>
<tr>
<th>Patent Number</th>
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<th>Inventors</th>
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NICHOLAS S. RIZZO, Primary Examiner.
UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,218,328
Seymour L. Shapiro, deceased, by
Florence M. Shapiro, as executrix, et al.

November 16, 1965

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 4, lines 44 to 50, formula (5) should appear as shown below instead of as in the patent:

![Formula Image]

Column 7, lines 44 to 54, formula (30) should appear as shown below instead of as in the patent:

![Formula Image]
column 10, lines 35 to 43, formula (52) should appear as shown below instead of as in the patent:

\[
\begin{align*}
&\text{O-CH}_2\text{-C-CH}_2\text{H}_5 \\
&\text{CH}_2\text{-CH} \\
&\text{CH}_2\text{-CH} \\
&\text{CH}_3
\end{align*}
\]

same column 10, lines 55 to 62, formula (54) should appear as shown below instead of as in the patent:

\[
\begin{align*}
&\text{O-CH}_2\text{-C-CH}_2\text{H}_5 \\
&\text{CH}_2\text{-CH} \\
&\text{CH}_2\text{-CH} \\
&\text{OH}
\end{align*}
\]

column 15, line 52, for "compessed" read -- compressed --.

Signed and sealed this 27th day of September 1966.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents