United States Patent Office

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

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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, amides, salts, acid addition salts and quaternary ammonium salts.

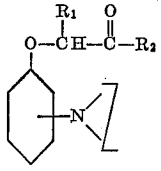
Another object of the invention is to provide compositions which are particularly effective for reducing the cholesterol level of blood, containing heterocyclic amino substituted phenoxyacetic acid compounds, esters, amides and related compounds.

In accordance with this invention, it has been determined that phenoxyacetic acid compounds having a heterocyclic amine group attached to the phenyl nucleus through a ring nitrogen atom are particularly effective as hypocholesteremic agents. The heterocyclic amine 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 amine 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 amine 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.

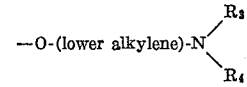
Suitable heterocyclic amino phenoxyacetic acid compounds of this invention are the phenoxyacetic acids and the esters and amides of the phenoxyacetic acids with lower alkyl alcohols, cycloalkyl alcohols, lower alkanolamines, ammonia and lower alkyl amines.

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



In the above formula, R_1 can be hydrogen or a lower alkyl group having from 1 to 6 carbon atoms, R_2 can be selected from the group consisting of hydroxy, lower alkoxy, cycloalkoxy preferably having from 5 to 7 carbon atoms, hydrazino, mono- and di- lower alkyl-hydrazino, amino of the formula

and lower oxyalkyl amino of the formula



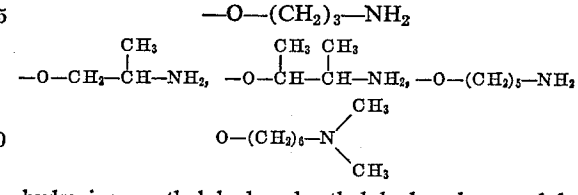
wherein R_3 and R_4 can each be hydrogen, lower alkyl, mono- and di-(lower alkyl)-amino-lower alkyl and amino-lower alkyl [e.g. $—C_3H_6—NH_2$].

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, =O. The total number of carbon atoms in the group

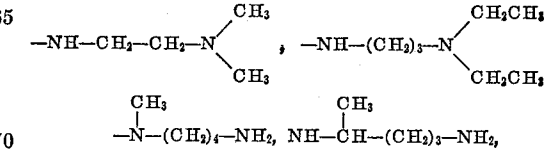
preferably does not exceed about 15.

It will be evident from the foregoing that the phenoxyacetic acid compounds of the invention are acids when R_2 is OH, esters when R_2 is alkoxy or cycloalkoxy or oxyalkylene, and amides when R_2 is amino. The term "acid compound" is used generically herein to refer to all of these subgenera of the invention.

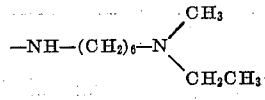
Thus, in the foregoing formula, R_1, R_3 and R_4 can each be, for example, hydrogen, methyl, ethyl, n-propyl, isopropl, n-butyl, iso-butyl, t-butyl and any of the pentyl and hexyl isomers. R_2 can, for example, be hydroxy, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, isobutoxy, t-butoxy and any of the isomeric pentoxy and hexoxy derivatives, cyclopentoxy, cyclohexoxy and cycloheptoxy, amino, monomethylamino, dimethylamino, monoethylamino, diethylamino, monoisopropylamino, diisopropylamino, mono-n-propylamino, di-n-propylamino, mono-n-butylamino, di-n-butylamino, mono-t-butylamino, di-t-butylamino, monopentylamino, dipentylamino, monohexylamino, dihexylamino, $—O—CH_2—CH_2—NH_2$,



hydrazino, methyl hydrazyl, ethyl hydrazyl, propyl hydrazyl,

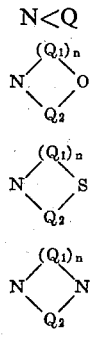


and



Thus

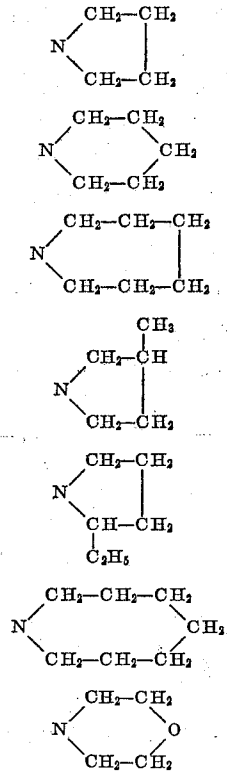
can be, for example

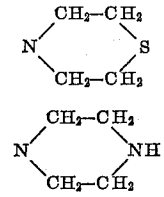


in which the Q groups are alkylene groups containing from one to about ten carbon atoms, *n* is zero or one and the total number of ring atoms in the group

ranges from about four to about ten. Representative

groups include





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

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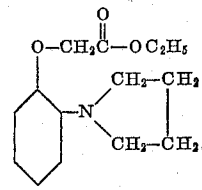

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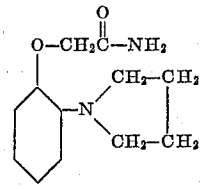

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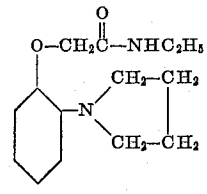

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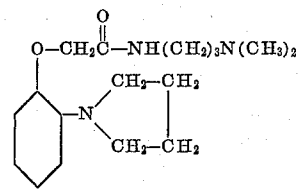

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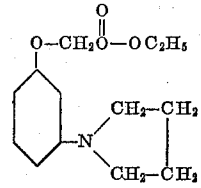

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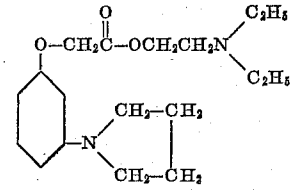

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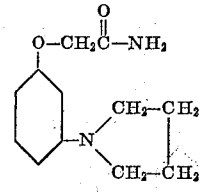

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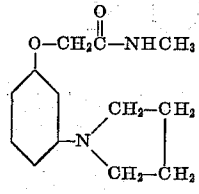

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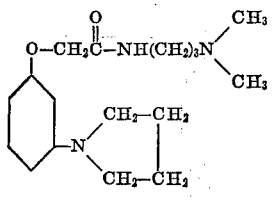

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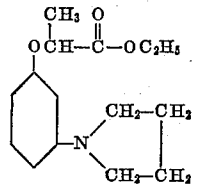

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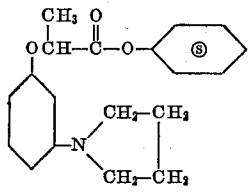

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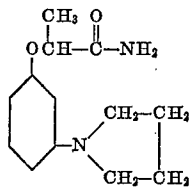

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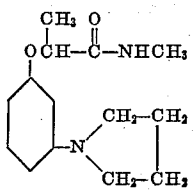

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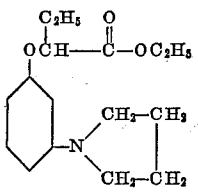

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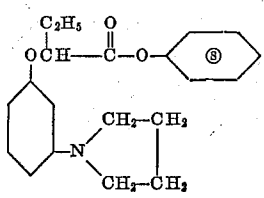

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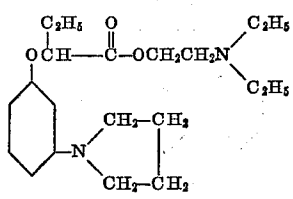

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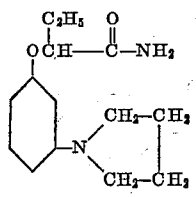

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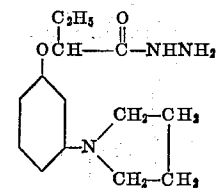

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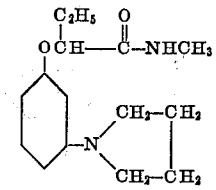

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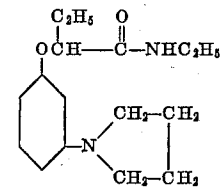

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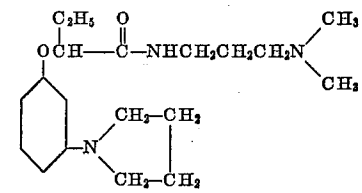

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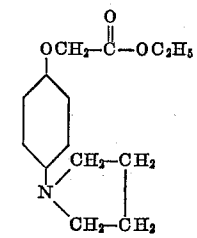

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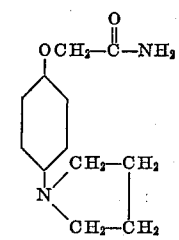

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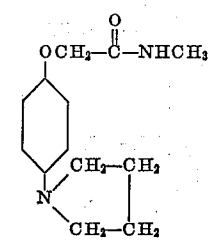

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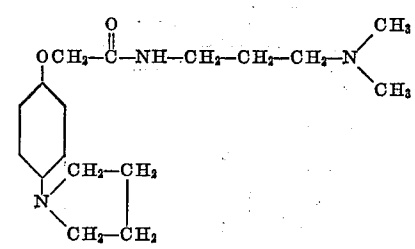
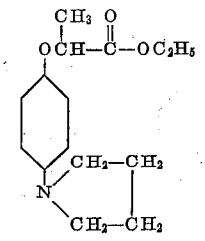
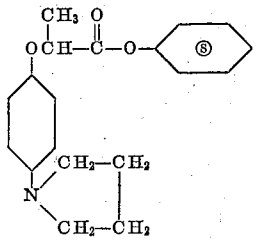
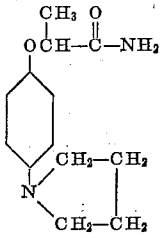
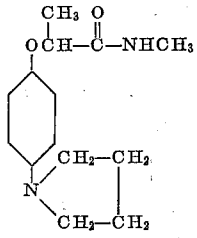
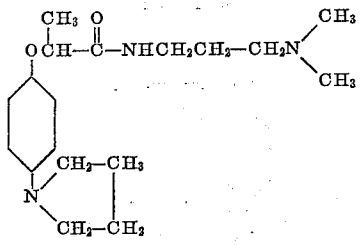


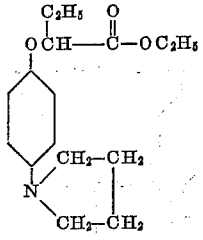
(26) 

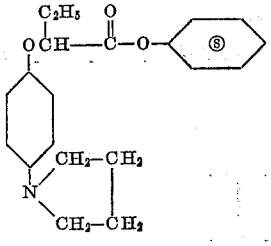
(27) 

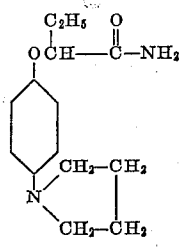
(28) 

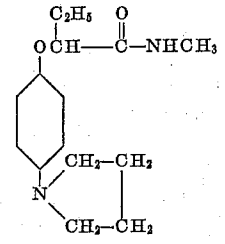
(29) 

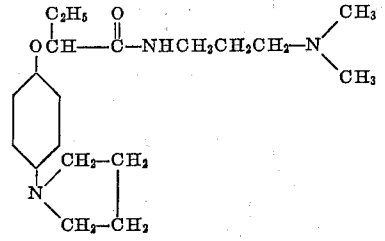
(30) 

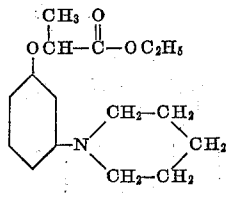
(31) 

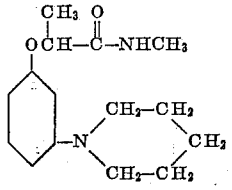
(32) 

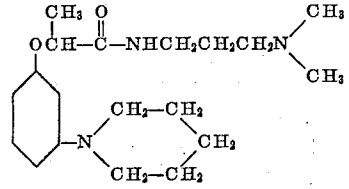
(33) 

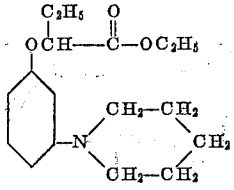
(34) 

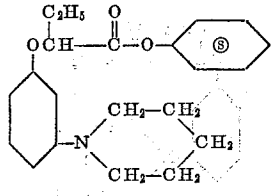
(35) 

(36) 

(37) 

(38) 

(39) 

(40) 

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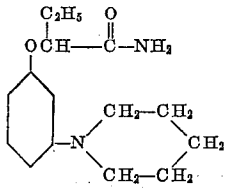

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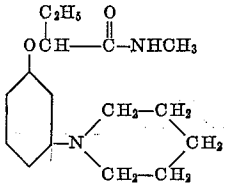

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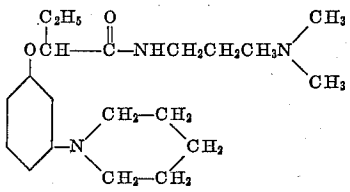

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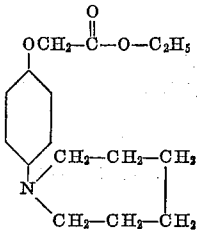

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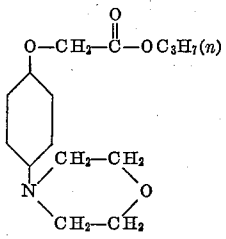

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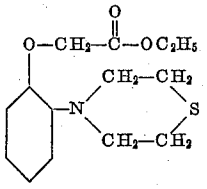

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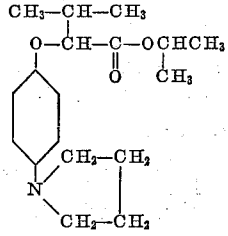

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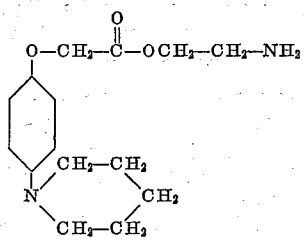

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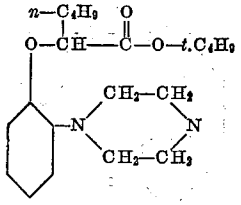

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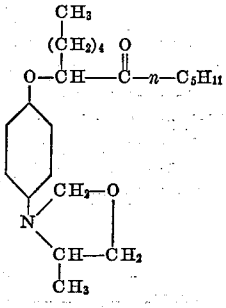

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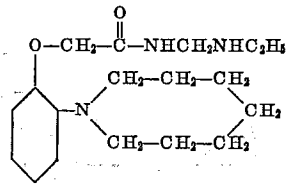

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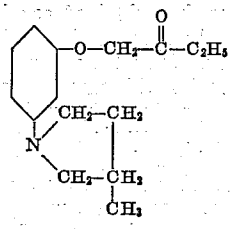

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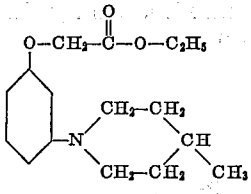

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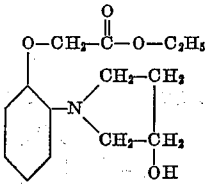

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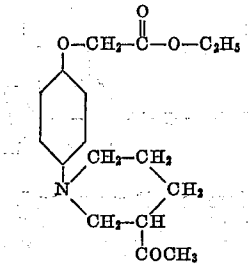

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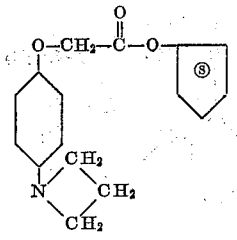
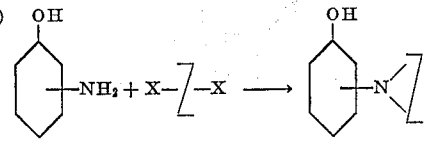
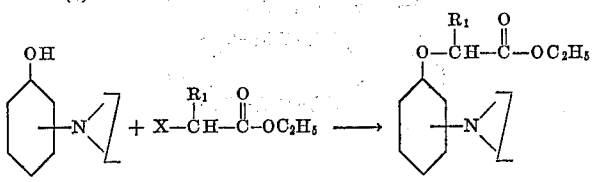


The compounds of this invention can be prepared by any of several procedures. The appropriate dihaloalkane can be condensed with an aminophenol to yield the required heteroamino phenol which can then be condensed with ethyl-alpha-halo acetates to give the substituted phenoxy acetates which can then be 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)



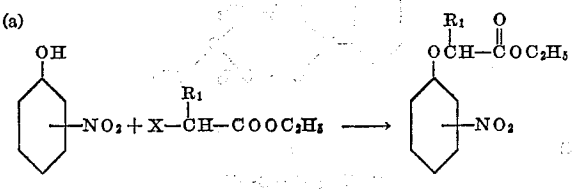
(b)



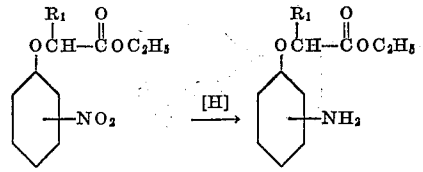
The acetate ester thus obtained can be hydrolyzed to form the acid, can be transesterified with an alcohol of the formula R_2OH to form the appropriate ester, can be reacted to form amides with ammonia and with primary or secondary amines, and with hydrazines. In an alternative procedure, the compounds of this invention can be prepared by condensing a nitrophenol with an ethyl-alpha-halo alkanoate, reducing the resultant nitrophenoxy acetate to the aminophenoxy acetate 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)



(b)



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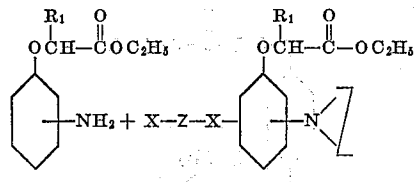
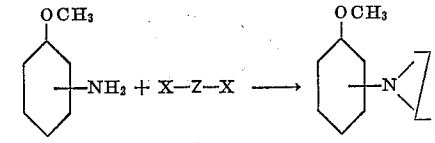


with further procedure as in Preparation I.

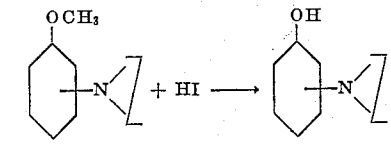
An alternative method of preparing the heteroaminophenols which can be used in Preparation I consists of ring closure with ortho, meta or para anisidine followed by cleavage of the ether with hydriodic acid. This procedure can be illustrated as follows:

(III)

(a)

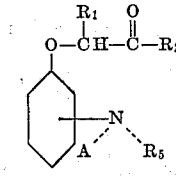


(b)



The resultant compounds can be reacted with any pharmaceutically acceptable inorganic or organic acid to form non-toxic pharmacologically acceptable acid addition salts such as hydrochlorides, hydrobromides, nitrates, sulfates, phosphates, acetates, formates, tartrates, malates, theophyllinates, 8-chloroetheophyllinates, 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, allyl bromide, ethyl bromoacetate, and the like, non-toxic pharmacologically acceptable quaternary salts of the novel compounds are readily prepared.

These quaternary salts can be represented by the formula



wherein R_5 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, octyl, allyl, pentyl, benzyl and carboethoxyalkyl such as carboethoxymethyl, and A is an inert non-toxic pharmacologically acceptable anion, such as bromide, iodide, chloride and p-toluenesulfonate.

When R_2 contains a nitrogen atom, the quaternary salt can be formed at that nitrogen atom or at both the R_2 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 phenoxyacetic 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 or alkyl sulfate can be added.

The acid addition salts are prepared by reacting equivalent quantities of the amino substituted phenoxyacetic 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 mls. of acetonitrile 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 gm. of the o-(1-pyrrolidinyl)anisole so prepared and 50 ml. of constant boiling hydriodic acid were refluxed together for 28 hours, permitting methyl iodide to distill out as formed. At the end of this time, the hydriodic 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°. 21.2 g. (0.13 mole) of this o-(1-pyrrolidinyl)phenol, 21.8 g. (0.13 mole) of ethyl bromoacetate, 18.5 g. (0.13 mole) of potassium carbonate and 200 ml. of acetone were refluxed with stirring for 40 hours. The solids were then filtered off, the filtrate evaporated down to a thick oil and this oil dissolved in benzene. This solution was extracted with several portions of dilute hydrochloric acid, and the resulting aqueous solution made basic again with 40% aqueous sodium hydroxide to yield an oil which was taken up in ether. The ethereal solution was then dried over anhydrous magnesium sulfate, the drying agent filtered off, the ether removed and the residue distilled to give 2.6 g. of ethyl-α-[o-(1-pyrrolidinyl)phenoxy]acetate, boiling at 136–139° C. at 0.25 mm. n_D^{20}=1.5465.

Anal.—Calc. for $C_{14}H_{19}NO_3$: C, 67.4; H, 7.7; N, 5.6. Found: C, 67.2; H, 7.6; N, 5.3.

EXAMPLE II

3-dimethylaminopropylamine (7.5 g., 0.075 mole), 3.8 g. (0.015 mole) of ethyl-α-[o-(1-pyrrolidinyl)phenoxy] acetate and 10 drops of 25% methanolic sodium methylate 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. (n_D^{20}=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. anhydrous potassium carbonate and 150 mls. of acetone. After refluxing and stirring for 7 hours, the solid was filtered off, 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 0.3 g. of platinum oxide was hydrogenated in a Parr hydrogenator at an initial 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 hydrogen chloride. Filtration yielded 38 g. melting at 125–135°. Recrystallization from acetonitrile gave 33 g. of ethyl 2-(m-aminophenoxy)acetate hydrochloride. A mixture of 8.0 g. (0.034 m.) of the ethyl 2-(m-aminophenoxy) acetate hydrochloride and 5.4 g. (0.051 m.) of anhydrous sodium carbonate and 30 mls. of acetonitrile was added while a solution of 7.4 g. (0.034 m.) of 1,4-dibromobutane in 20 mls. of acetonitrile 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-pyrrolidinylphenoxy)acetate.

Anal.—Calc. for $C_{14}H_{19}NO_3$: 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 I

Compound No. (as listed above)	Recrystallization Solvent	Melting Point (° C.) [1]
2	Acetonitrile	133–134
3	Hexane	61– 62
7	Ethanol	156
8	Hexane	96– 99
12	Isopropanol	134–137
13	do	109–111
17	do	148–150
18	Hexane	101–102
19	do	113–116
20	do	78– 81
22	Ethanol	57– 58
23	Methanol	211
24	Ethanol	175
25	Hexane	97– 98
28	Ethanol	164
29	Heptane	115
33	Ethanol	161
34	Heptane	144
37	Hexane	88– 89
41	do	88– 89
42	do	63– 64

[1] Taken on Fisher-Johns Melting Point Block and corrected.

EXAMPLE VI

Additional compounds were prepared in acordance with the procedure of Examples I and II tested. The boiling points and/or refractive indices of representative compounds are listed in Table II.

Table II

Compound No. (as listed above)	Boiling Point, ° C.	Pressure, mm.	n_D^{20}
1	128–131	0.2	
4	178–182	0.005	1.5474
5	150–154	0.2	
6	186–190	0.15	
9	186–189	0.04	1.5570
10	142–144	0.15	
11	178–180	0.25	1.5426
14	128–133	0.02	
15	164–168	0.07	1.5387
16	178–182	0.10	
21	184–188	0.07	1.5430
26	138–143	0.04	1.5390
27	176–180	0.04	1.5409
30	190–195	0.03	
31	146–150	0.03	1.5340
32	180–183	0.03	1.5360
35	190–196	0.04	
36	140–144	0.02	1.5335
38	179–182	0.01	1.5414
39	156–160	0.02	
40	172–176	0.01	1.5742
43	200–204	0.01	

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

In addition to the heterocyclic amino phenoxyacetic acid compound, the hypocholesteremic 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 administerable 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 300 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 hypocholesteremic 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 hypocholesteremic 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 o-(1-pyrrolidinyl)phenoxy acetate 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 betalactose (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:

	Grams
Active ingredient	308
Sugar	308
Lactose	177
Starch	98
Dextrin	50
Talcum	10
Stearic acid	10

Starch paste q.s. to make 1000.

The above mix was comphessed 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:

	Grams
Active ingredient	25
Sodium hydroxide	5.74
Benzyl alcohol	5

Water, pyrogen-free, q.s. to 500 ml.

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-rheumatic effect, butazolidin or antipyrine or related compounds for their anti-pyretic and anti-phlogistic effects, hydrocortisone or prednisolone or one of its equivalent corticosteroids for their anti-rheumatic, anti-inflammatory and anti-phlogistic 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 hypocholesteremic compositions can be sterilized and can contain auxiliary substances such as buffering agents, stabilizing agents, wetting agents and emulsifying agents.

To illustrate the therapeutic utility 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, 40 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 hypocholsteremic response is indicated in Table III. In this table, the compound is identified by its number in the list above. The $LD_{min.}$ 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 hypocholesteremia).

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% hypocholesteremia.

Table III

HYPOCHOLESTEREMIC EFFECT OF REPRESENTATIVE COMPOUNDS

Compound No.	$LD_{min.}$, mg./kg. s.c.	Percent Hypocholesteremia	
		48 hrs.	72 hrs.
1	1,000	22	30
8	1,000	49	34
9	400	15	27
11	1,000	29	34
16	500	17	33
18	750	41	31
22	350	26	34
23	1,000	17	43
24	1,000	31	40
28	500	13	13
33	1,000	12	27

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 hypocholesteremic response.

It is evident from Table III that the compounds of this invention show substantial hypocholesteremic activity at dosage levels substantially below the minimum lethal doses. A considerable reduction of cholesterol levels is

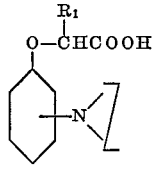
obtained at substantially 1/30 of the $LD_{min.}$ for many of the compounds.

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



wherein R_1 is selected from the group consisting of hydrogen and lower alkyl, and

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

is pyrrolidino.

3. A compound in accordance with claim 1 wherein

is piperidino.

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NICHOLAS S. RIZZO, *Primary Examiner.*

UNITED STATES PATENT OFFICE

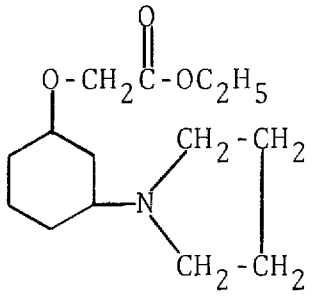
CERTIFICATE OF CORRECTION

Patent No. 3,218,328 November 16, 1965

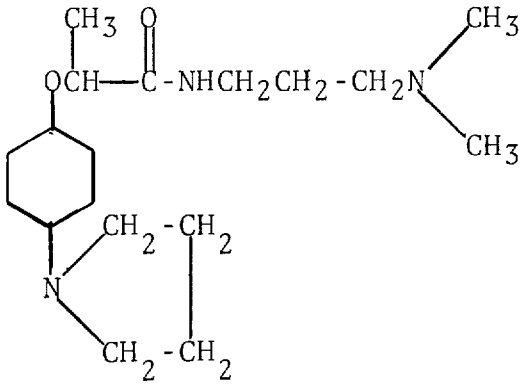
Seymour L. Shapiro, deceased, by
Florence M. Shapiro, as executrix, et al.

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.

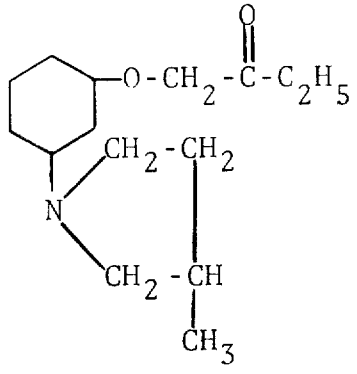
Column 4, lines 44 to 50, formula (5) should appear as shown below instead of as in the patent:



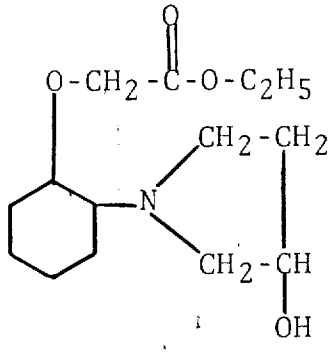
column 7, lines 44 to 54, formula (30) should appear as shown below instead of as in the patent:



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



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



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

Signed and sealed this 27th day of September 1966.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents