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3,585,199

## {4-[3-(POLYAZAHETEROCYCLIC)ALKANOYL]PHENOXY}ALKANOIC ACIDS

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No Drawing. Filed May 25, 1967, Ser. No. 641,122

Int. Cl. C07d 57/48

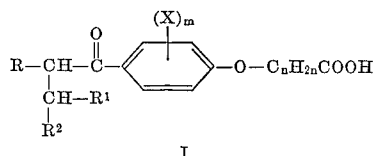
U.S. Cl. 260-256

3 Claims

### ABSTRACT OF THE DISCLOSURE

{4-[3-(polyazaheterocyclic)alkanoyl]phenoxy}alkanoic acids, a class of compounds possessing diuretic and saluretic properties for use in treating conditions associated with electrolyte and fluid retention and prepared by the addition of a polyazaheterocycle to a [4-(2-alkylideneacyl)phenoxy]alkanoic acid in the presence of a base followed by acidification to precipitate the product.

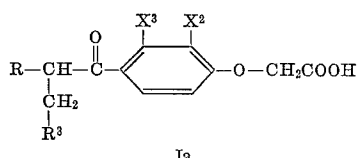
This invention relates to {4-[3-(polyazaheterocyclic)alkanoyl]phenoxy}alkanoic acids (I) and a method of preparing the same, of the following general formula:



wherein R is a straight or branched chain lower alkyl radical such as methyl, ethyl, propyl, isopropyl and the like or trifluoromethyl substituted lower alkyl such as 2,2,2-trifluoroethyl, 2,2,2-trifluoroisopropyl, etc.; R<sup>1</sup> is hydrogen or a straight or branched chain lower alkyl radical; R<sup>2</sup> is a polyazaheterocyclic radical selected from the group consisting of 1-pyrazolyl, 1-imidazolyl, 1,2,4-triazol-1 (or 4) -yl, 1,2,3-triazol-1 (or 2) -yl, 1 (or 2) -tetrazolyl, 1-benzimidazolyl, 1 (or 2) -indazolyl, 1(1H) [or 3(3H)]-imidazo[4,5-b]-pyridyl and the homologous lower alkyl derivatives of the aforesaid radicals as, for example, the methyl, ethyl, propyl, isopropyl, etc. derivatives and 1,2,3,6-tetrahydro-1,3-di-lower alkyl-2,6-dioxopurin-7 (or 9) -yl; X is hydrogen, a straight or branched chain lower alkyl radical, halogen such as chlorine, bromine, iodine or fluorine, or, when taken together, two X radicals on adjacent carbon atoms of the benzene ring may be joined to form a 1,3-butadienylene linkage, i.e. —CH=CH—CH=CH—; m is an integer from 1 to 4 and n is an integer from 1 to 4.

The products of this invention are diuretic and saluretic agents which can be used in the treatment of conditions associated with electrolyte and fluid retention and hypertension. When administered in therapeutic dosages, in conventional vehicles, the instant products effectively reduce the amount of sodium and chloride ions in the body, lower dangerous excesses of fluid levels to acceptable limits and, in general, alleviate conditions usually associated with edema.

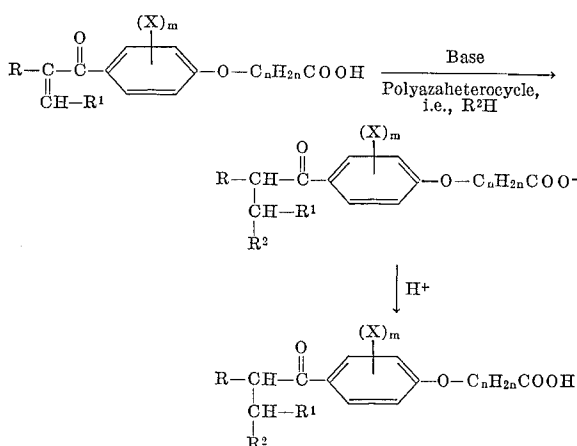
A preferred embodiment of the invention, i.e., compounds which possess the greatest diuretic and saluretic activity, are the {4-[3-(polyazaheterocyclic)alkanoyl]phenoxy}acetic acids (Ia) which have the following general formula:



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wherein R is a straight or branched chain lower alkyl radical such as methyl, ethyl, propyl, isopropyl and the like or trifluoromethyl substituted lower alkyl such as 2,2,2-trifluoroethyl, 2,2,2-trifluoroisopropyl, etc.; R<sup>3</sup> is a polyazaheterocyclic radical selected from 1-pyrazolyl, 1 (or 3) -1H (or 3H)-imidazo[4,5-b]-pyridyl, 1-imidazolyl, 1,2,4-triazol-1 (or 4) -yl and the homologous lower alkyl derivatives of the aforesaid radicals and 1,2,3,6-tetrahydro-1,3-di-lower alkyl-2,6-dioxopurin-7 (or 9) -yl; and X<sup>2</sup> and X<sup>3</sup> are hydrogen, a straight or branched chain lower alkyl radical, halogen or taken together with the carbon atoms of the benzene ring to which they are attached they may be joined to form a 1,3-butadienylene linkage.

The instant compounds are prepared by the addition of a polyazaheterocycle to a [4-(2-alkylideneacyl)phenoxy]alkanoic acid, preferably in the presence of a base, followed by acidification, viz:



wherein R, R<sup>1</sup>, R<sup>2</sup>, X, m and n are the same as described hereinbefore and H<sup>+</sup> is the cation derived from an organic or inorganic acid such as hydrochloric acid, sulfuric acid, nitric acid and the like. If the base is employed it forms a salt with the acid and also catalyzes the addition of the polyazaheterocycle to the double bond as shown above. The salt of the product formed is usually water soluble but, upon acidification, precipitates out as the acid product which can be purified by recrystallization from a suitable solvent. Such bases as sodium bicarbonate, sodium carbonate, sodium hydroxide and the like may be used. Recrystallization can be carried out preferably using polar solvents such as lower alkanols (e.g. ethanol and isopropyl alcohol) and dimethylformamide or from mixtures of the foregoing with non-polar solvents (e.g. ether). Optimally, a large excess of the polyazaheterocycle is used, the reaction time is fairly long and it is carried out at lower temperatures, preferably at or below room temperature, and at a pH of about 7-10, preferably towards the higher pH. Dimethylformamide may be used to increase the solubility of the starting acid and/or the salt formed therefrom upon addition of the base.

Illustrative, but non-limitative, examples of the preparation of the instant compounds are as follows:

### EXAMPLE 1

{2,3-dichloro-4-[1-oxo-2-ethyl-3-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurin-7 (or 9) -yl)propyl]phenoxy}acetic acid

A solution of [2,3-dichloro-4-(2-methylenebutyl)-phenoxy]acetic acid (6.06 g., 0.02 mole) in water (100 ml) is treated with sufficient 5% aqueous sodium hydrox-

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ide to maintain a pH of 7.1. Theophylline (3.6 g., 0.02 mole) is added and the solution is stirred at 25° C. for 16 hours. The solution is filtered and acidified with concentrated hydrochloric acid (2 ml.) to yield 5.4 g. (56%) of {2,3-dichloro-4-[1-oxo-2-ethyl-3-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurin-7(or 9)-yl)propyl]phenoxy}acetic acid which after recrystallization from ethanol (60 ml.) melts at 205–207° C.

Analysis for  $C_{20}H_{20}Cl_2N_4O_6$ .—Calculated (percent): C, 49.70; H, 4.17; N, 11.59; Cl, 14.67. Found (percent): C, 49.80; H, 4.31; N, 11.38; Cl, 14.44.

## EXAMPLE 2

{2,3-dichloro-4-[2-ethyl-3-(1-imidazolyl)propionyl]phenoxy}acetic acid hydrochloride

A solution of [2,3-dichloro-4-(2-methylenebutyryl)-phenoxy]acetic acid (9.1 g., 0.03 mole) and sodium bicarbonate (2.52 g., 0.03 mole) in water (150 ml.) is treated with imidazole (2.04 g., 0.03 mole) and stirred at room temperature for 16 hours. The water is removed by distillation at reduced pressure at 50° C. and the residue is dissolved in ethanol (50 ml.). Ether (100 ml.) and concentrated aqueous hydrochloric acid (4 ml.) are added causing the precipitation of sodium chloride which is removed by filtration. The filtrate is dried over anhydrous sodium sulfate, filtered and heated with additional ether (500 ml.) with precipitates 5.9 g. (41%) of {2,3-dichloro-4-[2-ethyl-3-(1-imidazolyl)propionyl]phenoxy}acetic acid hydrochloride, which after recrystallization from a mixture of isopropyl alcohol and ether melts at 169–173° C.

Analysis for  $C_{16}H_{17}Cl_2O_4$ .—Calculated (percent): C, 47.14; H, 4.20; N, 6.87. Found (percent): C, 46.97; H, 4.08; N, 6.86.

## EXAMPLE 3

{2,3-dichloro-4-[2-(1-pyrazolylmethyl)butyryl]phenoxy}acetic acid

To a solution of sodium bicarbonate (2.52 g., 0.03 mole) in water (150 ml.) is added [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (9.09 g., 0.03 mole). Then pyrazole (2.04 g., 0.03 mole) is added and the resulting solution is allowed to stand at room temperature. After 66 hours, the clear reaction solution is made acid to Congo red paper by the addition of 6 N hydrochloric acid. The resulting precipitate that separates is recrystallized from ethanol to give white needles; the yield is 8.92 g. (80%). M.P. 170–171°. Further purification by recrystallization from acetonitrile gives {2,3-dichloro-4-[2-(1-pyrazolylmethyl)butyryl]phenoxy}acetic acid melting at 174–175°.

Analysis for  $C_{16}H_{16}Cl_2N_2O_4$ .—Calculated (percent): C, 51.77; H, 4.34; N, 7.55. Found (percent): C, 51.92; H, 4.31; N, 7.76.

## EXAMPLE 4

{2,3-dichloro-4-[2-(1-benzimidazolymethyl)butyryl]phenoxy}acetic acid

To a solution of sodium bicarbonate (2.52 g., 0.03 mole) in water (150 ml.), is added [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (9.09 g., 0.03 mole). Then benzimidazole (3.54 g., 0.03 mole) is added and the resulting solution is stirred at room temperature. After 45 hours, the reaction solution is filtered and the clear filtrate is made acid to Congo red paper by the addition of 6 N hydrochloric acid. The white solid that separates is collected by filtration, washed with water and dried; the yield is 11.68 g. Recrystallization from ethanol gives 9.82 g. (78%) of {2,3-dichloro-4-[2-(1-benzimidazolymethyl)butyryl]phenoxy}acetic acid in the form of white prisms, M.P. 186–187°.

Analysis for  $C_{20}H_{18}Cl_2N_2O_4$ .—Calculated (percent): C, 57.02; H, 4.31; N, 6.65. Found (percent): C, 57.01; H, 4.15; N, 6.81.

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## EXAMPLE 5

{2,3-dichloro-4-[2-(1-(or 2)-indazolymethyl)butyryl]phenoxy}acetic acid

To a solution of sodium bicarbonate (2.52 g., 0.03 mole) in water (100 ml.) is added [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (9.09 g., 0.03). Then a suspension of indazole (3.54 g., 0.3 mole) in water (50 ml.) is added. Solution is effected by the addition of water (450 ml.), adjusting the pH to 8.0 with aqueous sodium hydroxide solution and warming on a steam bath for 5 minutes. The resulting solution is allowed to stand at room temperature. After 48 hours, the clear reaction solution is acidified to a pH of 4.0 by the addition of 6 N hydrochloric acid. The solid that separates is isolated by filtration, washed with water and dried; the yield is 12.00 g. After grinding under ether, filtering and washing with ether, there is obtained 7.66 g. of a white solid, M.P. 148–151°. Further purification by recrystallization from isopropyl alcohol gives 6.34 g. (50%) of {2,3-dichloro-4-[2-1(or 2)-indazolymethyl]butyryl]phenoxy}acetic acid in the form of white needles, M.P. 163–164°.

Analysis for  $C_{20}H_{18}Cl_2N_2O_4$ .—Calculated (percent): C, 57.02; H, 4.31; N, 6.65. Found (percent): C, 57.34; H, 4.39; N, 6.97.

## EXAMPLE 6

1(or 3-[2-(2,3-dichloro-4-carboxymethoxybenzoyl)butyl]-1H(or 3H)-imidazo[4,5-b]pyridine

To a solution of sodium bicarbonate (2.52 g., 0.03 mole) in water (100 ml.) is added [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (9.09 g.; 0.03 mole). Then a solution of 4-azabenzimidazole (3.57 g.; 0.03 mole) in water (50 ml.) is added and the resulting solution is allowed to stand at room temperature in a nitrogen atmosphere. After 45 hours, the clear reaction solution is treated with one equivalent of 6 N hydrochloric acid to give a pH of 3.0. The solid that separates is isolated by filtration, washed with water and dried; the yield is 11.77 g. Recrystallization from a dimethylformamide-ethanol mixture gives 7.31 g. (58%) of a 1(or 3)-[2-(2,3-dichloro-4-carboxymethoxybenzoyl)butyl]-1H(or 3H)-imidazo-[4,5-b]pyridine in the form of a white solid, M.P. 196–197°.

Analysis for  $C_{19}H_{17}Cl_2N_3O_4$ .—Calculated (percent): C, 54.04; H, 4.06; N, 9.95. Found (percent): C, 53.71; H, 4.37; N, 9.77.

## EXAMPLE 7

{2,3-dichloro-4-[2-(1,2-triazol-1(or 4)-ylmethyl)butyryl]phenoxy}acetic acid

To a solution of sodium bicarbonate (2.52 g., 0.03 mole) in water (150 ml.) is added [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (9.09 g., 0.03 mole). Then 1,2,4-triazole (2.07 g., 0.03 mole) is added and the resulting solution is stirred at room temperature in a nitrogen atmosphere. After 45 hours, the clear reaction solution is made acid to Congo red paper by the addition of 6 N hydrochloric acid. The precipitate that separates is isolated by filtration and recrystallized from ethanol to give 7.82 g. (70%) of {2,3-dichloro-4-[2-(1,2,4-triazol-1(or 4)-ylmethyl)butyryl]phenoxy}acetic acid in the form of white needles; a second recrystallization from ethanol gives 6.97 g. of the product which melts at 170–171°.

Analysis for  $C_{15}H_{15}Cl_2N_3O_4$ .—Calculated (percent): C, 48.40; H, 4.06; N, 11.29. Found (percent): C, 48.44; H, 3.97; N, 11.20.

## EXAMPLE 8

{2,3-dichloro-4-[2-(3,5-dimethyl-1-pyrazolylmethyl)butyryl]phenoxy}acetic acid

To a solution of sodium bicarbonate (2.52 g., 0.03 mole) in water (100 ml.) is added [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (9.09 g., 0.03

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mole). Then a suspension of 3,5-dimethylpyrazole (2.88 g., 0.03 mole) in water (75 ml.) is added. The resulting solution is adjusted to a pH of 7.0 by the addition of aqueous sodium hydroxide solution and then allowed to stand at room temperature. After 45 hours, the clear reaction solution is acidified to a pH of 3.0 by the addition of 6 N hydrochloric acid. The solid that separates is removed by filtration, washed with water and dried; the yield is 10.87 g. After grinding under ether, filtering and washing with ether, there is obtained 9.77 g. (82%) of {2,3-dichloro-4-[2-(3,5-dimethyl-1-pyrazolyl-methyl) butyryl]phenoxy}acetic acid in the form of white prisms, M.P. 154–155°.

Analysis for  $C_{18}H_{20}Cl_2N_2O_4$ .—Calculated (percent): C, 54.15; H, 5.05; N, 7.02. Found (percent): C, 54.04; H, 5.19; N, 17.08.

## EXAMPLE 9

{2,3-dichloro-4-[2-ethyl-3-(1-imidazolyl)butyryl]phenoxy}acetic acid

To a solution of sodium bicarbonate (2.52 g., 0.03 mole) in water (100 ml.) is added [2,3-dichloro-4-(2-ethylidenebutyryl)phenoxy]acetic acid (9.52 g. 0.03 mole). Then a solution of imidazole (2.04 g., 0.03 mole) in water (50 ml.) is added and the resulting solution is allowed to stand at room temperature. After 8 days, the clear reaction solution is acidified to a pH of 3.0 by the addition of 6 N hydrochloric acid. The precipitate that separates is isolated and recrystallized from isopropyl alcohol-ethyl acetate mixture. Further purification by recrystallization from ethanol gives 1.44 g. (13%) of {2,3-dichloro-4-[2-ethyl-3-(1-imidazolyl)butyryl]phenoxy}acetic acid in the form of white prisms, M.P. 156–157°.

Analysis for  $C_{17}H_{18}Cl_2N_2O_4$ .—Calculated (percent): C, 53.00; H, 4.71; N, 7.27. Found (percent): C, 52.84; H, 4.91; N, 7.17.

## EXAMPLE 10

{2,3-dichloro-4-[2-ethyl-3-(1-imidazolyl)propionyl]phenoxy}acetic acid hydrochloride

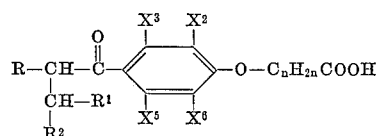
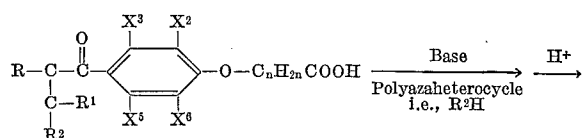
A solution of 2,3-dichloro-4-(2-methylenebutyryl)-phenoxy}acetic acid (9.1 g., 0.03 mole) and sodium bicarbonate (2.52 g., 0.03 mole) in water (150 ml.) is treated with imidazole (2.04 g., 0.03 mole) and stirred at room temperature for 16 hours. The water is distilled from the reaction at reduced pressure at 50° C. and the residue is dissolved in ethanol (50 ml.), ether (100 ml.)

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and concentrated aqueous hydrochloric acid (4 ml.) causing precipitation of sodium chloride which is removed by filtration. The filtrate is dried over anhydrous sodium sulfate, filtered and heated with additional ether (500 ml.) which precipitates 5.0 g. (41%) of {2,3-dichloro-4-[2-ethyl-3-(1-imidazolyl)propionyl]phenoxy}acetic acid hydrochloride which melts at 169–173° C. after recrystallization from a mixture of isopropyl alcohol and ether.

Analysis for  $C_{16}H_{17}Cl_3O_4$ .—Calculated (percent): C, 47.14; H, 4.20; N, 6.87. Found (percent): C, 46.97; H, 4.08; N, 6.86.

In a manner similar to that described in Example 1 for the preparation of {2,3-dichloro-4-[1-oxo-2-ethyl-3-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurin-7 (or 9)-yl)propyl]phenoxy}acetic acid all of the {4-[3-(polyazaheterocyclic)alkanoyl]phenoxy}alkanoic acid products of the invention may be obtained. Thus, by substituting the appropriate polyazaheterocycle and [4-(2-alkylideneacyl)phenoxy]alkanoic acid for the theophylline and [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid reactants recited in Example 1 and following the procedure described therein all of the products of the invention may be obtained. The following equation illustrates the reaction of Example 1 and, together with Table I, illustrates the starting materials of the instant process and the corresponding products (Ib) derived therefrom:



Ib

TABLE I

| Example | R                                                | R <sup>1</sup>                 | R <sup>2</sup>                                                  | X <sup>2</sup>   | X <sup>3</sup>   | X <sup>4</sup>   | X <sup>5</sup>   | —C <sub>n</sub> H <sub>2n</sub> —         |
|---------|--------------------------------------------------|--------------------------------|-----------------------------------------------------------------|------------------|------------------|------------------|------------------|-------------------------------------------|
| 11      | —CH <sub>2</sub> —CF <sub>3</sub>                | H                              | 4-methyl-1-pyrazolyl                                            | —CH <sub>3</sub> | —CH <sub>3</sub> | H                | H                | —CH <sub>2</sub> —                        |
| 12      | —C <sub>2</sub> H <sub>5</sub>                   | H                              | 1,2,3-triazol-1 (or 2) -yl                                      | H                | Cl               | H                | H                | Same as above.                            |
| 13      | Same as above                                    | H                              | 5-methyl-1 (or 3) - benzimidazolyl                              | —CH=CH—CH=CH—    |                  | H                | H                | Do.                                       |
| 14      | do                                               | H                              | 1 (1H) [or 3(3H)]-imidazo [4,5-b] pyridyl                       | —CH <sub>3</sub> | —CH <sub>3</sub> | H                | H                | Do.                                       |
| 15      | —CH(CH <sub>3</sub> )(CF <sub>3</sub> )          | H                              | 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurin-7 (or 9) -yl     | H                | —CH <sub>3</sub> | H                | H                | Do.                                       |
| 16      | —C <sub>2</sub> H <sub>5</sub>                   | H                              | 5-methyl-1(1H) [or 3(3H)] imidazo[4,5-b]pyridyl                 | H                | Cl               | H                | H                | Do.                                       |
| 17      | Same as above                                    | H                              | 1,2,3,6-tetrahydro-1,3-diethyl-2,6-dioxopurin-7 (or 9) -yl      | —CH <sub>3</sub> | %                | —CH <sub>3</sub> | —CH <sub>3</sub> | Do.                                       |
| 18      | do                                               | H                              | 6-ethyl-1(1H) [or 3(3H)] imidazo[4,5-b]pyridyl                  | H                | Cl               | H                | H                | Do.                                       |
| 19      | —CH(CH <sub>3</sub> ) <sub>2</sub>               | H                              | 3 (or 5) -methyl-1, 2,4-triazol-1 (or 4) -yl                    | Cl               | Cl               | H                | H                | Do.                                       |
| 20      | —C <sub>2</sub> H <sub>5</sub>                   | H                              | 4-methyl-1-imidazolyl                                           | H                | Cl               | Cl               | H                | —CH[CH—(CH <sub>3</sub> ) <sub>2</sub> ]— |
| 21      | Same as above                                    | H                              | 5-methyl-1 (or 2) -indazolyl                                    | —CH <sub>3</sub> | —CH <sub>3</sub> | —CH <sub>3</sub> | —CH <sub>3</sub> | —CH <sub>2</sub> —                        |
| 22      | do                                               | H                              | 4-methyl-1,2,3-triazol-1 (or 2) -yl                             | Br               | Cl               | H                | H                | Same as above.                            |
| 23      | —CH <sub>3</sub>                                 | —C <sub>2</sub> H <sub>5</sub> | 1 (or 2) -tetrazolyl                                            | H                | Cl               | H                | H                | Do.                                       |
| 24      | —(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub> | H                              | 1,2,3,6-tetrahydro-1-methyl-3-ethyl-2,6-dioxopurin-7 (or 9) -yl | H                | Cl               | H                | H                | Do.                                       |

The products of the invention can be administered in a wide variety of therapeutic dosages in conventional vehicles as, for example, by oral administration in the form of a capsule or tablet as well as by intravenous injection. Also, the dosage of the products may be varied over a wide range as, for example, in the form of capsules or scored tablet containing 5, 10, 20, 25, 50, 100, 150, 250 and 500 milligrams, i.e., from 5 to about 500 milligrams, of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. These dosages are well below the toxic or lethal dose of the products.

A suitable unit dosage form of the products can be prepared by mixing 100 mg. of a {4-[3-(polyazaheterocyclic)alkanoyl]phenoxy}alkanoic acid with 94 mg. of lactose and 6 mg. of magnesium stearate, and placing the 200 mg. mixture into a No. 3 gelatin capsule. Similarly, by employing more of the active ingredient and less lactose, other dosage forms can be put up in No. 3 gelatin capsules and, should it be necessary to mix more than 200 mg. of ingredients together, larger capsules may be employed. Compressed tablets, pills or other desired unit dosages can be prepared to incorporate the instant compounds by conventional methods and, if desired, can be made up as elixirs or as injectable solutions by methods well known to pharmacists.

It is also within the scope of this invention to combine two or more of the compounds of this invention in a unit dosage form or to combine one or more of the compounds with other known diuretics and saluretics or with other desired therapeutic and/or nutritive agents in dosage unit form.

The following example is illustrative of the preparation of the representative dosage form:

#### EXAMPLE 25

Dry-filled capsules containing 100 mg. of active ingredient per capsule

|                                                                                                                                    | Mg. per capsule |
|------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| {2,3 - dichloro - 4 - [1-oxo-2-ethyl-3-(1,2,3,6-tetrahydro-1,3-dimethyl - 2,6 - dioxopurin-7 (or 9) -yl)propyl]phenoxy}acetic acid | 100             |
| Lactose                                                                                                                            | 94              |
| Magnesium stearate                                                                                                                 | 6               |
| Capsule size No. 3                                                                                                                 | 200             |

The {2,3 dichloro - 4[1 - oxo - 2 - ethyl-3-(1,2,3,6-tetrahydro-1,3-dimethyl - 2,6 - dioxopurin - 7 ( or 9 ) -yl)-propyl]phenoxy}acetic acid is reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for 10 minutes and then filled into No. 3 dry gelatin capsules.

Similar dry-filled capsules can be prepared by replacing the active ingredient of the above example by any of the other novel compounds of this invention.

It will be understood that this invention also includes the salts, esters and amides of the instant acids which are compatible with the body system and whose pharmacological properties will not cause adverse physiological effects. The salts may be formed as indicated in the foregoing examples except that the final acidification step is omitted. They may also be made by the direct addition of a suitable base to the {4-[3-(polyazaheterocyclic)alkanoyl]phenoxy}acetic acid. Suitable bases which can be used to form the salts are, for example, the alkali metal and alkaline earth metal hydroxides, carbonates, bicarbonates, etc., ammonia, primary, secondary and tertiary amines such as monoalkylamines, dialkylamines, trialkylamines, nitrogen containing heterocyclic amines, for example, piperidine, etc.

Suitable esters and amides include, for example, the alkyl esters, the dialkylaminoalkyl esters and the amide,

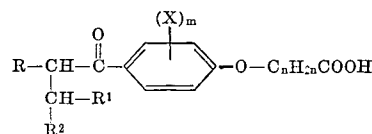
monoalkylamides, dialkylamides and heterocyclic amide derivatives as, for example, amides derived from heterocyclic amines as pyrrolidine, piperidine, morpholine, etc. The esters and amides are prepared by the same procedures set forth in the examples hereinbefore except that the [4-(2-alkylidenacyl)phenoxy]alkanoic acid is first converted to the desired ester or amide as the starting material. In this case the addition of the base is used solely to raise the pH since there is no salt formation. Also it is often necessary to add a solvent such as a lower alkanol, dimethylformamide and the like. They also may be prepared from the acid halide derivatives of the {4-[3-(polyazaheterocyclic)alkanoyl]phenoxy}alkanoic acids by reaction with a suitable alcohol, ammonia, monoalkylamine, dialkylamine or heterocyclicamine.

The foregoing and other equivalent methods for the preparation of the salts, esters and amide derivatives of the instant products will be apparent to those having ordinary skill in the art and, to the extent that the said derivatives are both nontoxic and physiologically acceptable to the body system, the said esters and amides are the functional derivatives of the corresponding acids.

It will be apparent from the foregoing description that the {4 - [3 - (polyazaheterocyclic)alkanoyl]phenoxy}alkanoic acids and their salts, esters and amides constitute a valuable class of compounds which have not hitherto been prepared. One skilled in the art will also appreciate that the processes disclosed in the above examples are merely illustrative and are capable of variation and modification without departing from the spirit of the invention.

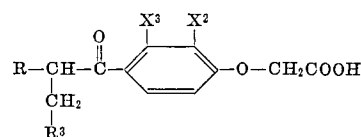
What is claimed is:

1. A compound of the general formula:



wherein R is selected from the group consisting of straight and branched chain lower alkyl, and trifluoromethyl substituted lower alkyl; R<sup>1</sup> is selected from the group consisting of hydrogen and straight and branched chain lower alkyl; R<sup>2</sup> is 1,2,3,6-tetrahydro-1,3-di-lower alkyl - 2,6-dioxopurin-7 (or 9) -yl; X is selected from the group consisting of hydrogen, halogen, and straight and branched chain lower alkyl, and when taken together two X radicals on adjacent carbon atoms of the benzene ring may be joined to form the 1,3-butadienylene linkage; m is an integer from 1-4 and n is an integer from 1-4 and the pharmaceutically acceptable salts thereof.

2. A compound of the general formula:



wherein R is selected from the group consisting of straight and branched chain lower alkyl; R<sup>3</sup> is 1,2,3,6-tetrahydro-1,3-di-lower alkyl-2,6-dioxopurin-7 (or 9) -yl; and X<sup>2</sup> and X<sup>3</sup> are selected from the group consisting of hydrogen, halogen and straight and branched chain lower alkyl, and

when taken together with the carbon atoms of the benzene ring to which they are attached they may be joined to form the 1,3-butadienylene linkage.

3. The compound of claim 2 wherein R is hydrogen, X<sup>2</sup> and X<sup>3</sup> are chlorine, and R<sup>3</sup> is 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurin-7 (or 9) -yl.

#### References Cited

##### UNITED STATES PATENTS

3,422,107 1/1969 Mohler et al. ----- 260—256 10

#### OTHER REFERENCES

Wagner and Zook, Synthetic, Organic Chemistry, New York, John Wiley & Sons, 1953, (pp. 672-673 relied on).

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U.S. Cl. X.R.

260—247.7K, 253, 2947G, 295R, 308A, D, R, 309, 309.2, 310C, 310R, 311, 520, 521R, 521A; 424—253

**UNITED STATES PATENT OFFICE**  
**CERTIFICATE OF CORRECTION**

Patent No. 3,585,199 Dated June 15, 1971

Inventor(s) Edward J. Cragoe, Jr.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In column 2, line 6, "pyridil" should be -- pyridyl --;  
In column 3, line 17, "solutio" should be -- solution --;  
In column 4, line 8, "0.3" should be -- 0.03 --;  
In column 4, title of Example No. 7, "1,2-triazol-"  
should be -- 1,2,4-triazol- --;  
In column 5, line 16, "N, 17.08" should be -- N, 7.08 --;  
In Table I, Example No. 17 between column headings  $X^2$   
and  $X^3$ , delete "%".

Signed and sealed this 16th day of November 1971.

(SEAL)

Attest:

EDWARD M. FLETCHER, JR.  
Attesting Officer

ROBERT GOTTSCHALK  
Acting Commissioner of Patents