United States Patent Office

3,466,370
Patented Sept. 9, 1969

3,466,370

PROCESS FOR TREATING HELMINTH INFESTATIONS USING BENZANILIDE DERIVATIVES AND COMPOSITIONS FOR USE THEREIN

Arthur William James Broome, Neville Stanton Crossley, and William Glynne Moss Jones, Macclesfield, England, assignors to Imperial Chemical Industries Limited, London, England, a corporation of Great Britain

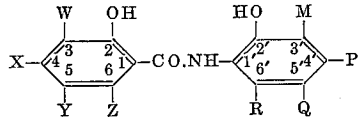
No Drawing. Filed July 30, 1964, Ser. No. 386,392
Claims priority, application Great Britain, Aug. 14, 1963, 32,130/63
Int. Cl. A01n 9/20
U.S. Cl. 424—233 11 Claims

ABSTRACT OF THE DISCLOSURE

Compositions and process for treating helminth infestations in animals wherein the active coponent is a benzanilide derivative such as 3,3'5,5',6-pentachloro-2,2'-dihydroxybenzanilide.

This invention relates to new pharmaceutical compositions and more particularly it relates to new pharmaceutical compositions which contain as the active ingredients benzanilide derivatives which are of value in the treatment of animals suffering from helminth infestations.

According to the invention we provide new pharmaceutical compositions characterised by the presence therein as active ingredient(s) of one or more benzanilide derivatives of the formula:



wherein W, X, Y, Z, M, P, Q and R, which may be the same or different, stand for hydrogen, chlorine or bromine provided that not more than two of W, X, Y and Z, and not more than two of M, P, Q and R, stand for hydrogen, or the pharmaceutically-acceptable salts thereof together with a pharmaceutically-acceptable diluent or carrier therefore.

Suitable benzanilide derivatives of the above stated formula are, for example

3,3',5,5',6'-pentachloro-2,2'-dihydroxybenzanilide,
3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide,
3,3',5,5',6,6'-hexachloro-2,2'-dihydroxybenzanilide,
3,3',4',5,5',6,6'-heptachloro-2,2'-dihydroxybenzanilide,
3,3'5,5'tetrachloro-2,2'-dihydroxybenzanilide and
3,3',4',5,5',6'-hexachloro-2,2'-dihydroxybenzanilide.

Suitable pharmaceutically-acceptable salts of the benzanilide derivatives used as active ingredients in the compositions of the present invention are, for example, alkali metal and alkaline earth metal salts, for example the sodium and calcium salts, and the salts of non-toxic organic bases, for example piperazine salts.

The pharmaceutical compositions of the invention may be designed either for oral or for parenteral administration and may be, for example, in the form of tablets, boluses, capsules, aqueous or oily solutions, aqueous or oily suspensions, emulsions, sterile injectable aqueous or oily solutions or suspensions, dispersible powders, premixes suitable for addition to animal foodstuffs or mixtures with animal foodstuffs.

The compositions of the invention may contain standard excipients known to the art to be useful in the formulation of such compositions and they may contain, for example, inert diluents, fillers, disintegrating agents, bacteriostats, bactericidal agents, sporicidal agents, stabilising agents, thickening agents, preservatives, wetting agents, dispersing agents, suspending agents and pharmaceutically-acceptable colouring agents. The compositions may also optionally contain other substances of veterinary utility, for example vitaminaceous materials, drugs of veterinary utility and mineral salts.

Suitable tablets and boluses may be formulated by admixture of the activet ingredient(s) with known pharmaceutical excipients, for example inert diluents, for example calcium carbonate, calcium phosphate or lactose, disintegrating agents, for example maize starch or alginic acid, binding agents, for example starch, gelatin or acacia mucilage, lubricating agents, for example magnesium stearate, stearic acid or talc, and wetting agents, for example the alkali metal salts of sulphonated dialkylnaphthalenes. Such tablets may optionally be coated by known techniques in order to delay disintegration in the upper gastrointestinal tract.

Compositions in the form of capsules may consist, for example, of gelatine capsules containing active ingredient(s) only or the active ingredient(s) in admixture with inert diluents, for example lactose or sorbitol, or, for example, in solution or suspension in a vegetable oil.

The aqueous suspensions, emulsions, oily solutions and suspensions of the invention may contain a sweetening agent, for example glycerol, dextrose or sucrose, and a flavouring agent, for example vanillin or orange extract, in order to provide a palatable product. The aqueous suspensions of the invention may also contain suitable suspending or thickening agents, for example sodium carboxymethylcellulose, wetting agents, for example condensation products of fatty alcohols with ethylene oxide, and suitable preservatives, for example methyl or propyl p-hydroxybenzoate.

The emulsion compositions of the invention may contain the active ingredient(s) dissolved in a suitable fat of vegetable or animal origin, for example arachis oil or cod liver oil, and may also contain sweetening agents and flavouring agents which may with advantage be essential oils. The emulsions may also contain emulsifying agents and dispersing agents, for example soya bean lecithin, polyoxyethylene sorbitan mono-oleate, gum acacia, gum tragacanth or casein, and preservatives, for example methyl or propyl p-hydroxybenzoate, and anti-oxidants, for example propyl gallate.

The oily solutions of the invention likewise may contain the active ingredient(s) in solution in a suitable fat of vegetable or animal origin, and may optionally contain flavouring agents to mask the taste and improve oral acceptability. The oily solutions may also contain sweetening agents, for example icing sugar, in which case the oil phase may in addition contain a suspending agent, for example beeswax, to maintain the redispersion properties of the suspension.

The sterile injectable aqueous suspensions of the invention may contain a suspending or thickening agent, for example sodium carboxymethylcellulose, and a wetting or dispersing agent, for example a phenolpolyethylene oxide condensate, for example the condensation product of octylcresol with about 8–10 moleucular proportions of ethylene oxide. The injectable oily solutions of the invention may be prepared from a non-toxic injectable fat or oil, for example arachis oil or ethyl oleate, and they may additionally contain gelling agents, for example aluminum stearate, to delay adsorption within the body. These aqueous and oily injectable preparations may contain preservatives such as methyl or n-propyl p-hydroxybenzoate or chlorobutenol.

The dispersable powders of the invention may contain the active ingredient(s) in admixture with suitable wetting, dispersing and suspending agents.

The premixes of the invention preferably contain between 1% and 25% by weight of the active ingredient(s) and may contain the active ingredient in admixture with non-toxic diluents or carriers, for example talc, kaolin, chalk, lactose, urea, corn or meal, ground oyster shells, distillers dried grains and edible vegetable substances, for example commercial animal foodstuffs.

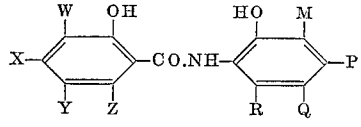
The mixtures with animal foodstuffs which are intended to be orally administered as such to domestic animals preferably contain between 0.01% and 2% by weight of the benzanilide derivative(s) used as active ingredient(s).

As stated above the pharmaceutical compositions of the invention may optionally additionally contain other substances of veterinary utility, for example drugs of veterinary utility. Suitable drugs of veterinary utility are, for example, anthelmintic drugs, for example, phenothiazine or methyridine and antibacterial drugs, for example benzylpenicillin, or sulphaguanidine.

The benzanilide derivatives used as active ingredients in the compositions of the present invention may be prepared by conventional methods, for example, by interaction of a reactive derivative of an appropriately substituted salicylic acid, for example the corresponding carboxylic chloride, and a suitably substituted o-aminophenol.

The compositions of the invention are effective in the treatment of helminth infestations, for example they are effective in removing liver fluke from domestic animals.

Accordingly, therefore, we provide a process for the treatment of helminth infestations in animals which comprises the administration thereto of an effective amount of one or more benzanilide derivatives of the formula:



wherein W, X, Y, Z, M, P, Q and R which may be the same or different, stand for hydrogen, chlorine or bromine provided that not more than two of W, X, Y and Z, and not more than two of M, P, Q and R, stand for hydrogen, or the pharmaceutically-acceptable salts thereof.

The process for the treatment of domestic animals, particularly sheep and cattle, by administration of the pharmaceutical compositions of the invention will depend upon the weight of the animal to be treated, the severity of the helminth infestations of the animal concerned and its general condition of health at the time of treatment. Administration of one or more doses at the rate of 5–100 mg. of active ingredient per kg. of body weight of animals and more particularly at a dosage rate of about 5–50 mg. of active ingredient per kg. of body weight of animal is satisfactory for the treatment of helminth infestations.

The invention is illustrated but not limited by the following examples in which the parts are by weight.

Example 1

10 parts of 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide, M.P. 224° C., are ball-milled with 90 parts of a solution obtained by dissolving in 1,000 parts of water 1 part of a condensate of 1 molecular proportion of octylcresol with about 9 molecular proportions of ethylene oxide and 1 part of polyglycerolricinoleate. There is thus obtained an aqueous suspension suitable for oral administration to domestic animals for the control of helminth infestations, for example liver fluke infestations.

Example 2

10 parts of 3,3',5,5',6,6'-hexachloro-2,2'-dihydroxybenzanilide, M.P. 226° C., are ball-milled with 90 parts of a solution obtained by dissolving in 1,000 parts of water 2.5 parts of a condensate of 1 molecular proportion of octycresol with about 9 molecular proportions of ethylene oxide. There is thus obtained a suspension suitable for administration to domestic animals for the treatment of helminth infestations, for example liver fluke infestations.

Example 3

100 parts of 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide are mixed with 1 part of sodium ligninsulphonate and 2 parts of the sodium salt of a butylated-naphthalene-sulphonic acid. The mixture thus obtained is reduced in particle size by passage through a mill. There is thus obtained a dispersible powder which can be added to water to form an aqueous suspension suitable for administration to domestic animals for the treatment of helminth infestations, for example liver fluke infestations.

Example 4

A mixture of 5 parts of 3,3',5,5',6,6'-hexachloro-2,2'-dihydroxybenzanilide and 95 parts of maize oil is stirred at 50° C. for 30 minutes and is then allowed to cool. There is thus obtained an oily solution suitable for administration to domestic animals for the treatment of helminth infestations, for example liver fluke infestations.

Example 5

A mixture of 100 parts of 3,3',4',5,5',6,6'-heptachloro-2,2'-dihydroxybenzanilide, M.P. 243° C., and 400 parts of calcium phosphate is passed through a 60-mesh sieve. To the mixture are then added 30 parts of starch in the form of an aqueous paste and the resultant mxiture is blended and compressed into granules. The granules are passed through a 10-mesh sieve and dried at 50° C. The dried granules are passed through a 20-mesh sieve and are then blended with a mixture of 5 parts of gum acacia and 20 parts of starch. To the mixture thus obtained there is added 10 parts of talc and 1 part of magnesium stearate and the resulting mixture is blended and then compressed into boluses which are suitable for administration to domestic animals for the treatment of helminth infestations, for example liver fluke infestations.

Example 6

A mixture of 100 parts of 3,3',5,5',6'-pentachloro-2,2'-dihydroxybenzanilide, 10 parts of maize starch, 10 parts of lactose and 2 parts of magnesium stearate is compressed into slugs and the slugs are passed through an 8-mesh sieve and then through a 16-mesh sieve. The granules thus obtained are then compressed into tablets which are suitable for administration to domestic animals for the treatment of helminth infestations, for example liver fluke infestations.

Example 7

2 parts of the piperazine salt of 3,3',5,5',6,6'-hexachloro-2,2'-dihydroxybenzanilide are intimately mixed with 80 parts of distillers dried grains. There is thus obtained a premix suitable for addition to animal foodstuffs for the treatment of helminth infestations, for example liver fluke infestations, in domestic animals.

Example 8

20 parts of 3,3'-5,5'-tetrachloro-2,2'-dihydroxybenzanilide are intimately mixed with 80 parts of wheat standard middling. There is thus obtained a premix suitable for addition to animal foodstuffs for the treatment of heminth infestations, for example liver fluke infestations, in domestic animals.

Example 9

100 parts of the calcium salt of 3,3',5,5',6,6'-hexachloro-2,2'-dihydroxybenzanilide are mixed with 1 part of sodium ligninsulphonate and 1 part of the sodium salt of a butylated-naphthalene-sulphonic acid. The mixture thus obtained is reduced in particle size by passage through a mill and there is thus obtained a dispersible powder which

can be added to water to form an aqueous suspension suitable for administration to domestic animals for the treatment of helminth infestations, for example liver fluke infestations.

Example 10

Three ewes, each with a liver fluke infestation, were treated by oral administration of 3,3',5,5',6,6'-hexachloro-2,2'-dihydroxybenzanilide as a suspension prepared as described in Example 2. The amount of drug administered was at the rate of 25 mg./kg. of body weight. During the six days following treatment the ewes expelled a total for each ewe respectively of 5, 34 and 86 dead adult lever fluke. The ewes were then killed. At post mortem no fluke were found in the livers of two of the animals while in the liver of the third ewe seventeen immature fluke but no adult fluke were found.

Example 11

25 parts of the piperazine salt of 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide are intimately mixed with 75 parts of distillers dried grains. There is thus obtained a premix suitable for addition to animal foodstuffs for the treatment of helminth infestations, for example liver fluke infestations.

Example 12

A mixture of 150 parts of the calcium salt of 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide and 350 parts of calcium phosphate is passed through a 60-mesh sieve. To the mixture are then added 25 parts of starch in the form of an aqueous paste and the resultant mixture is blended and compressed into granules. The granules are passed through a 10-mesh sieve and dried at 50° C. The dried granules are further passed through a 20-mesh sieve and are mixed with a mixture of 5 parts of gum acacia and 20 parts of starch. To the mixture thus obtained there are added 18 parts of talc and 1 part of magnesium stearate and the resulting mixture is blended and then compressed into tablets which are suitable for administration to domestic animals for the treatment of helminth infestation, for example liver fluke infestations.

Example 13

10 parts of 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide are dissolved in a solution of 2 parts of sodium hydroxide in 50 parts of water. Dilute hydrochloric acid is then added to the solution until the pH of the solution is 10 and the solution is thereafter filtered through a Seitz filter and the filtrate is filled into ampoules. There is thus obtained a sterile solution suitable for parenteral administration to animals for the treatment of helminth infestations.

Example 14

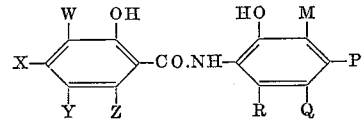
Two ewes, each with a liver fluke infestation, were treated by oral administration of 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide as a suspension prepared as described in Example 1. The drug was administered at the rate of 10 mg./kg. of body weight in the case of the first ewe and 15 mg./kg. of body weight in the case of the second ewe. During the six days following treatment the first ewe expelled a total of 94 fluke and the second ewe expelled a total of 100 fluke. The ewes were then killed. At post mortem no fluke were found in the livers of either ewe.

Example 15

Three cows, each with a liver fluke infestation, were treated by oral administration of 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide as a suspension prepared as described in Example 1. The amount of drug administered was at the rate of 10 mg./kg. of body weight. During the three days following treatment the cows expelled a total for each cow respectively of 94, 100 and 88 flukes The cows were killed six days following treatment. No flukes were found in the livers of the animals on post mortem examination.

What we claim is:

1. A composition for the treatment of helminth infestations comprising as active ingredient, an anthelmintically effective amount of at least one compound selected from the group consisting of benzanilide derivatives of the formula:



wherein W, X, Y, Z, M, P, Q and R are selected from the group consisting of hydrogen, chlorine and bromine provided that at least two of W, X, Y and Z are selected from the group consisting of chlorine and bromine and that at least two of M, P, Q and R are selected from the group consisting of chlorine and bromine, and the alkali metal, alkaline earth metal and nontoxic pharmaceutically-acceptable organic base salts thereof, together with a pharmaceutically-acceptable carrier therefor.

2. A composition as claimed in claim 1, wherein the benzanilide derivatives are selected from the group consisting of 3,3',5,5',6'-pentachloro-2,2'-dihydroxybenzanilide, 3,3',5,5',6-pentachloro-2,2'-dihydroxybenzanilide, 3,3',5,5',6,6' - hexachloro - 2,2'-dihydroxybenzanilide, 3,3',4',5,5',6,6' - heptachloro-2,2'-dihydroxybenzanilide, 3,3',5,5'-tetrachloro - 2,2'-dihydroxybenzanlide and 3,3',4',5,5',6'-hexachloro-2,2'-dihydroxybenzanilide.

3. A composition, as claimed in claim 1, which additionally contains another drug of veterinary utility selected from the group consisting of phenothiazine, methyridine, benzylpenicillin and sulphaguanidine.

4. A composition as claimed in claim 1 wherein the salts are selected from the group consisting of sodium, calcium and piperazine salts.

5. A composition as claimed in claim 1 which is in a form selected from the group consisting of tablets, boluses, capsules, aqueous and oily solutions, dispersible powders, and mixtures with animal feeds.

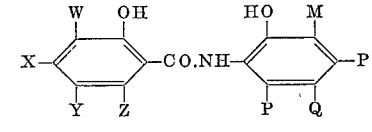
6. A composition as claimed in claim 1 which contains between 1% and 25% by weight of the active ingredient.

7. A composition as claimed in claim 5, wherein the active ingredient is in admixture with at least one member of the group consisting of talc, kaolin, chalk, lactose, urea, corn or meal, ground oyster shells, distiller dried grains and edible vegetable substances.

8. A composition as claimed in claim 5, which is a mixture with an animal feed and contains between 0.01% and 2% by weight of active ingredient.

9. A composition as claimed in claim 5 which is an aqueous suspension and which contains as active ingredient 3,3',5,5',6 - pentachloro - 2,2' - dihydroxybenzanilide together with a wetting agent which is a condensation produce of a fatty alcohol with ethylene oxide.

10. Process for the treatment of helminth infestations in animals which comprises the administration thereto of an anthelmintically-effective amount of at least one compound selected from the group consisting of benzanilide derivatives of the formula:



wherein W, X, Y, Z, M, P, Q and R are selected from the group consisting of hydrogen, chlorine and bromine provided that at least two of W, X, Y and Z are selected

from the group consisting of chlorine and bromine and at least two of M, P, Q and R are selected from the group consisting of chlorine and bromine, and the alkali metal, alkaline earth, and nontoxic pharmaceutically-acceptable organic base salts thereof, the amount of anthelimintically-effective compound being in the range of 5 to 100 mg. per kg. of body weight of the animal treated.

11. A process as claimed in claim **10** wherein there is administered an anthelmintically-effective amount of 3,3′, 5,5′,6-pentachloro-2,2′-dihydroxybenzanilide.

References Cited

UNITED STATES PATENTS

3,305,575	2/1967	Debarre	260—454
2,703,322	3/1955	Bindler.	
3,072,573	1/1963	Spacht.	

FRANK CACCIAPAGLIA, JR., Primary Examiner

U.S. Cl. X.R.

424—247, 263, 271, 324